SUPPLEMENTARY MATERIAL

Reversible Thiazolidine Exchange: A New Reaction Suitable for Dynamic Combinatorial Chemistry.

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Experimental procedures and spectral data for all new compounds. ¹H-NMR and chiral HPLC of DCL reactions. Copies of ¹H and ¹³C NMR spectra of **4b**, **5b**, **6aa**, **6ab**, **6ba** and **6bb**, copies of NOE diff spectra of **6aa**.

General Methods.

Reactions were monitored by analytical thin layer chromatography (TLC) 0.25 mm Silica gel plastic sheets (Macherey-Nagel, Polygram® SIL G/UV 254). Flash chromatography on Silica gel 60 (J. T. Baker, 40 μ m average particle diameter) was used to purify the crude reaction mixtures. NMR spectra were recorded at 400 MHz 100 MHz (^1H -NMR, ^{13}C -NMR) using a Bruker AVANCE at 21 $^\circ\text{C}$. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity, coupling constant and integration. IR spectra were obtained on a Perkin Elmer 1310 and FTIR 8101A Shimadzu spectrometer, units cm^{-1} . High resolution mass spectra were measured on VG AutoSpect spectrometer (EIS mode). Melting points were determined using a Laboratory Devices Gallenkamp apparatus. Optical rotations were measured using a Kruss Optronic GmbH P8000 polarimeter with a 0.5-mL cell (concentration c given as g/100 mL). Liquid chromatography was performed with a Shimadzu LC 20 AT provided with UV (SPD-M20A) detection. All solvents were purified according to literature procedures. All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographic and spectroscopic (^1H and ^{13}C -NMR) pure compounds. Diastereomeric excess was calculated based on ^1H RMN spectra.

Typical procedure for the synthesis of thiazolidines (Scheme 1). (2*RS*,4*R*) Ethyl-2-(4-chlorophenyl) thiazolidine-4-carboxylate (3b**).** To a stirred solution of L-cysteine ethyl ester hydrochloride (880 mg, 4.7 mmol) in dry EtOH (10 mL)

was added Et_3N (464 mg, 4.7 mmol) and *p*-chlorobenzaldehyde (1 g, 10.3 mmol). The reaction mixture was stirred for 3 hours and the solvent was evaporated. The residue was purified by chromatography on SiO_2 (EtOAc/Hexanes, 3:1) to afford compound **3b** (1.1g, 86%) as a colorless oil, diastereomeric ratio (40:60): ^1H NMR (CDCl_3), δ 1.24–1.34 (m, 6 H), 2.60 (t, J = 12.2 Hz, 1 H_{NH}), 2.89 (t, J = 7.8 Hz, 1 H_{NH}), 3.11 (dd, J = 8.9, 10.3 Hz, 1 H), 3.16 (dd, J = 6.2, 10.6 Hz, 1 H), 3.38 (dd, J = 7.1, 10.6 Hz, 1 H), 3.47 (dd, J = 7.1, 10.3 Hz, 1 H), 3.93–4.00 (m, 1 H), 4.08–4.15 (m, 1 H), 4.23–4.30 (m, 4 H), 5.52 (d, J = 12.2 Hz, 1 H), 5.80 (d, J = 7.8 Hz, 1 H)*, 7.28–7.36 (m, 4 H), 7.41–7.49 (m, 4 H); ^{13}C NMR (CDCl_3) δ 14.14, 37.45, 38.18, 39.29, 61.69, 61.78, 65.62, 69.92, 71.6, 128.31, 128.47, 128.89, 134.44, 136.72, 140.17, 171.05, 171.60. * Minor component.

(2*RS*,4*R*) Ethyl-2-phenylthiazolidine-4-carboxylate (3a**).** Prepared in 85% yield as a colorless oil analogous to the route described for **3b**, diastereomeric ratio (40:60). ^1H NMR (CDCl_3), δ 1.30–1.33 (m, 6 H), 2.67 (bs, 1 H_{NH}), 3.11 (dd, J = 8.9, 10.2 Hz, 1 H),

3.19 (dd, J = 6.0, 10.6 Hz, 1 H), 3.40 (dd, J = 7.1, 10.6 Hz, 1 H) 3.47 (J = 7.1, 10.2 Hz, 1 H), 3.98 (dd, J = 7.2, 8.9 Hz, 1 H), 4.19 (dd, J = 7.2, 8.9 Hz, 1 H), 4.22–4.30 (m, 4 H), 5.57 (s, 1 H), 5.83 (s, 1 H)*, 7.48–7.54 (m, 6 H),

7.48-7.54 (m, 4 H); ^{13}C NMR (CDCl_3) δ 14.12, 30.06, 38.16, 39.24, 61.56, 61.68, 64.33, 65.65, 70.78, 72.21, 72.61, 126.86, 127.42, 127.81, 128.38, 128.65, 128.69, 138.10, 141.27, 171.10, 171.69. * Minor component.

(2RS,4R) Ethyl 2-(4-nitrophenyl)thiazolidine-4-carboxylate (3d). Prepared in 90% yield as a yellow oil analogous to the route described for **3b**, diastereomeric ratio (43:57). ^1H NMR (CDCl_3), δ 1.31-1.35 (m, 6 H), 2.68 (t, $J = 12.1$, 1 H_{NH})*, 3.11 (t, $J = 7.8$ Hz, 1 H_{NH}), 3.13-3.19 (m, 2 H), 3.40 (dd, $J = 6.8$, 10.6 Hz, 1 H) 3.51 (dd, $J = 7.1$, 10.3 Hz, 1 H), 4.00-4.10 (m, 2 H), 4.25-4.33 (m, 4 H), 5.62 (d, $J = 12.1$ Hz, 1 H)*, 5.91 (d, $J = 7.8$ Hz, 1 H), 7.65-7.74 (m, 4 H), 8.18-8.26 (m, 4 H). * Minor component.

(2RS,4R) Ethyl 2-(4-methylphenyl)thiazolidine-4-carboxylate (3e). Prepared in 90% yield as a pale yellow oil analogous to the route described for **3b**, diastereomeric ratio (32:68). ^1H NMR (CDCl_3), δ 1.29-1.33 (m, 6 H), 2.33 (s, 3H), 2.35 (s, 3H), 2.66 (bs, 1 H_{NH}), 3.10 (dd, $J = 9.0$, 10.3 Hz, 1 H), 3.19 (dd, $J = 5.8$, 10.6 Hz, 1 H), 3.39 (dd, $J = 7.2$, 10.6 Hz, 1 H) 3.46 (dd, $J = 7.1$, 10.3 Hz, 1 H), 3.96 (dd, $J = 7.2$, 9.0 Hz, 1 H), 4.20 (dd, $J = 5.8$, 7.1 Hz, 1 H), 4.26 (m, 4 H), 5.54 (s, 1 H), 5.80 (s, 1 H)*, 7.13-7.19 (m, 4 H), 7.36-7.42 (m, 4 H). * Minor component.

(2RS,4R) Ethyl 2-(3-methylphenyl)thiazolidine-4-carboxylate (3f). Prepared in 88% yield as a pale yellow oil analogous to the route described for **3b**, diastereomeric ratio (33:67). ^1H NMR (CDCl_3), δ 1.30-1.34 (m, 6 H), 2.35 (s, 3H), 2.37 (s, 3H), 2.66 (t, $J = 11.6$ Hz, 1 H_{NH}), 2.83 (bs, 1 H_{NH}), 3.10 (dd, $J = 9.1$, 10.2 Hz, 1 H), 3.19 (dd, $J = 5.9$, 10.6 Hz, 1 H), 3.40 (dd, $J = 7.1$, 10.6 Hz, 1 H) 3.47 ($J = 7.1$, 10.2 Hz, 1 H), 3.9-3.40 (m, 1 H), 4.19-4.31 (m, 5 H), 5.54 (d, $J = 11.6$ Hz, 1 H), 5.80 (s, 1 H)*, 7.07-7.34 (m, 8 H). * Minor component.

(2RS,4R) Ethyl 2-(4-methoxyphenyl)thiazolidine-4-carboxylate (3d). Prepared in 90% yield as a colorless oil analogous to the route described for **3b**, diastereomeric ratio (30:70). ^1H NMR (CDCl_3), δ 1.29-1.33 (m, 6 H), 3.12 (dd, $J = 8.8$, 10.3 Hz, 1 H), 3.21 (dd, $J = 5.8$, 10.6 Hz, 1 H), 3.40 (dd, $J = 7.2$, 10.6 Hz, 1 H) 3.46 (dd, $J = 7.2$, 10.3 Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.97 (dd, $J = 7.2$, 8.8 Hz, 1 H), 4.20 (dd, $J = 5.8$, 7.2 Hz, 1 H), 4.24-4.29 (m, 4 H), 5.54 (s, 1 H), 5.78 (s, 1 H)*, 6.65-6.91 (m, 4 H), 7.41-7.47 (m, 4 H). * Minor component.

Synthesis of Methyl (2*RS*,4*RS*)-2-(4-chlorophenyl)-5,5-dimethylthiazolidine-4-carboxylate (4b). To a stirred solution of L/D-penicillamine methyl ester hydrochloride¹ (200 mg, 1.0 mmol) in dry EtOH (6 mL) was added Et₃N (101 mg, 1.0 mmol) and *p*-chlorobenzaldehyde (280 mg, 10.3 mmol). The reaction mixture

was stirred overnight and the solvent was evaporated. The residue was purified by chromatography on SiO₂ (EtOAc/*n*-hexanes, 1:9) to afford compound **4b** (120 mg, 43%) as a colorless oil, diastereomeric ratio (74/26): Major component: ¹H NMR (CDCl₃), δ 1.35 (s, 3 H), 1.72 (s, 3 H), 3.09 (t, *J* = 12.3 Hz, 1 H_{NH}), 3.65-3.75 (m, 1 H), 3.79 (s, 3 H), 5.64 (d, *J* = 12.3 Hz, 1 H), 7.27-7.35 (m, 2 H), 7.41-7.46 (m, 2 H); ¹³C NMR (CDCl₃) δ 27.14, 29.09, 52.20, 59.84, 69.30, 74.65, 127.97, 128.39, 128.80, 128.93, 134.35, 137.18, 169.57.

Minor component: ¹H NMR (CDCl₃), δ 1.30 (s, 3 H), 1.60 (s, 3 H), 3.09 (bs, 1 H_{NH}), 3.78 (s, 1 H), 3.79 (s, 3 H), 5.81 (s, 1 H), 7.27-7.35 (m, 2 H), 7.41-7.46 (m, 2 H); ¹³C NMR (CDCl₃) δ 28.01, 28.38, 52.18, 60.28, 67.52, 72.69, 127.97, 128.39, 128.80, 128.93, 133.07, 141.67, 170.07.

Methyl (2*RS*,4*RS*)-5,5-dimethyl-2-phenylthiazolidine-4-carboxylate (4a).² Prepared in 79% yield as a colorless oil analogous to the route described for **4b**, diastereomeric ratio 78/22.

Major component: ¹H NMR (CDCl₃), δ 1.39 (s, 3 H), 1.75 (s, 3 H), 3.19 (bs, 1 H_{NH}), 3.72-3.80 (m, 1 H), 4.11 (s, 3 H), 5.73 (bs, 1 H), 7.27-7.59 (m, 4 H).

Minor component: ¹H NMR (CDCl₃), δ 1.34 (s, 3 H), 1.65 (s, 3 H), 3.19 (bs, 1 H_{NH}), 3.72-3.80 (m, 1 H), 3.81 (s, 3 H), 5.90 (s, 1 H), 7.27-7.59 (m, 4 H).

Typical procedure for thiazolidine exchange (Table 1 and 2). A solution of compound **3a** (21 mg, 0.09 mmol) and *p*-Cl-benzaldehyde (12.3 mg, 0.09 mmol) in a mixture of acetate buffer at pH 4 (63mL) and MeOH (27mL) was stirred at rt for 2 d. The pH was raised to 7 by adding a saturated solution of NaHCO₃ and the reaction mixture was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo (temperature should never exceed 22°C). The residue was analyzed by ¹H NMR to determine the product ratio, and purified on SiO₂ (AcOEt/*n*-hexanes 1:7) to give a mixture of **3a** + **3b** (23 mg, 98% yield).

Thiazolidine exchange at 35 °C, 1 d: Prepared analogous to the typical procedure for thiazolidine exchange described above, but the temperature of the mixture was 35 °C during 1 d. The residue was analyzed by ¹H NMR

¹ Prepared according to: Wondrak, G. T.; Jacobson, M. K.; Jacobson, E. L. *J. Pharm. Expt. Ther.* **2005**, 316, 805-814.

² Pinho e Melo, T.; Soares, M. I. L.; Nunes, C. M. *Tetrahedron* **2007**, 63, 1833-1841.

to determine the product ratio, and purified on SiO₂ (AcOEt/*n*-hexanes 1:7) to give a mixture of **3a** (29%) + **3b** (35%) + **2** (18%).

Thiazolidine exchange at 35 °C, 2 d: Prepared analogous to the typical procedure for thiazolidine exchange described above, but the temperature of the mixture was 35°C during 2 d. The residue was analyzed by ¹H NMR to determine the product ratio, and purified on SiO₂ (AcOEt/*n*-hexanes 1:7) to give a mixture of **3a** (17%) + **3b** (32%) + **2** (16%).

Typical procedure for thiazolidine library exchange (Scheme 2). A solution of compound **3a** (51 mg, 0.215 mmol), *p*-Cl-benzaldehyde (30.3 mg, 0.215 mmol), *p*-MeO-benzaldehyde (29.3 mg, 0.215 mmol), *p*-Me-benzaldehyde (26 mg, 0.215 mmol) and *m*-Me-benzaldehyde (26 mg, 0.215 mmol) in a mixture of acetate buffer at pH 4 (150 mL) and MeOH (65 mL) was stirred at rt for 2 days. The pH was raised to 7 by adding a saturated solution of NaHCO₃ and the reaction mixture was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo (temperature should never exceed 22°C). The residue was analyzed by ¹H NMR to determine the product ratio **3a** (21%), **3b** (20%), **3c** (11%), **3d** (24%) and **3e** (24%). After 4d, the distribution remained unchanged and the purification on SiO₂ (AcOEt/*n*-hexanes 1:9) gave a mixture of **3a**, **3b**, **3c**, **3d**, **3e** (62 mg, 93% yield) + **2** (2mg, 7% yield).

Typical procedure for thiazolidine metathesis (Scheme 3). A solution of compound **3a** (13 mg, 0.053 mmol) and **4b** (15 mg, 0.053 mmol) in a mixture of acetate buffer at pH 4 (40 mL) and MeOH (13 mL) was stirred at rt for 2 d. The pH was raised to 7 by adding a saturated solution of NaHCO₃ and the reaction mixture was extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo (temperature should never exceed 22 °C). The residue was analyzed by ¹H NMR to determine the product ratio as: **3a** (36%), **4b** (30%), **3b** (12%), **4a** (22%). Purification of the residue led to a mixture of **3a**, **4b**, **3b**, **4a** (26mg, 90% yield) + **2** (1mg, 7% yield) + penicillamine methyl ester (1 mg, 3% yield).

Typical procedure for the preparation of aminoalcohols. (2*RS*,4*R*)-4-(Hydroxymethyl)-2-(4-chlorophenyl)thiazolidine (5b**).³** To a stirred solution of **3b** (2 g, 7.4 mmol) in MeOH (30 mL) was added NaBH₄ (1.7g, 44 mmol) portion wise at

0°C. After the addition was complete, the mixture was allowed to reach room temperature and stirred for 4 hours. The solvent was removed under reduced pressure. The residue was poured into water and the pH was adjusted to 7 by adding HCl (1M) and extracted with AcOEt (5 x 30 mL). The combined organic layers were dried (MgSO₄),

³ Mahler, S. G.; Serra G. L.; Manta, E. *Synth. Commun.* **2005**, *35*, 1481–1492.

filtered and concentrated. The residue was purified by chromatography to afford compound **5b** (1.5 g, 88% yield) as a colorless oil. IR (KBr) ν = 3364, 2930, 1491, 1092, 1015, 820 cm^{-1} .

(2R,4R)-4-(Hydroxymethyl)-2-(4-chlorophenyl)thiazolidine (2R-5b): ^1H NMR (CDCl_3), δ 2.85 (dd, J = 4.8, 10.6 Hz, 1 H), 3.22 (dd, J = 7.0, 10.6 Hz, 1 H), 3.60 (dd, J = 8.2, 11.2 Hz, 1 H), 3.65 (dd, J = 5.1, 11.2 Hz, 1 H), 3.85 (dddd, J = 4.8, 4.9, 7.0, 8.2 Hz, 1 H), 5.52 (s, 1 H), 7.29-7.33 (m, 2 H), 7.41-7.45 (m, 2 H).

(2S,4R)-4-(Hydroxymethyl)-2-(4-chlorophenyl)thiazolidine (2S-5b): ^1H NMR (CDCl_3), δ 2.96 (t, J = 9.8, 1 H), 3.13 (dd, J = 6.2, 9.8 Hz, 1 H), 3.45 (dddd, J = 3.8, 4.8, 6.2, 9.8 Hz, 1 H), 3.75 (dd, J = 4.9, 11.2 Hz, 1 H), 3.97 (dd, J = 3.8, 11.2 Hz, 1 H), 5.54 (s, 1 H), 7.29-7.33 (m, 2 H), 7.41-7.45 (m, 2 H); ^{13}C NMR (CDCl_3) δ 36.85, 37.00, 62.12, 62.54, 65.05, 66.58, 69.67, 71.52, 128.60, 128.67, 128.71, 129.42, 133.91, 134.13, 137.80, 138.38; HRMS calculated for $\text{C}_{10}\text{H}_{12}\text{ClNOS}$ [$\text{M}^+ - \text{H}$]: 229.0328, found: 229.0334.

(2R,4R)-4-(Hydroxymethyl)-2-phenylthiazolidine (5a). Prepared in 82 % yield as a white solid analogous to the route described for **5b**.

(2R,4R)-4-(Hydroxymethyl)-2-phenylthiazolidine: ^1H NMR (CDCl_3), δ 2.86 (dd, J = 4.7, 10.6 Hz, 1 H), 3.24 (dd, J = 6.9, 10.6 Hz, 1 H), 3.62 (dd, J = 8.2, 11.0 Hz, 1 H), 3.66 (dd, J = 5.0, 11.0, 1 H), 3.88 (dddd, J = 5.0, 5.0, 6.9, 8.2, 1 H), 5.53 (s, 1 H), 7.31-7.34 (m, 2 H), 7.43-7.47 (m, 2 H).

(2S,4R)-4-(Hydroxymethyl)-2-phenylthiazolidine: ^1H NMR (400MHz, CDCl_3), δ 2.98 (t, J = 9.8 Hz, 1 H), 3.15 (dd, J = 6.3, 9.8 Hz, 1 H), 3.48 (dddd, J = 3.7, 4.7, 6.3, 9.8 Hz, 1 H), 3.78 (dd, J = 5.0, 11.2 Hz, 1 H), 3.99 (dd, J = 3.7, 11.2 Hz, 1 H), 5.56 (s, 1 H), 7.31-7.34 (m, 2 H), 7.43-7.47 (m, 2 H).

(2R,4R)-4-(Hydroxymethyl)-2-phenylthiazolidine: ^{13}C NMR (CDCl_3) δ 36.73, 36.90, 62.07, 62.36, 65.05, 66.58, 70.24, 72.0, 127.15, 127.25, 128.28, 128.49, 128.56, 128.57, 138.94, 139.42.

Typical procedure for preparation of fused thiazolidine-oxazolidine heterocycles (Scheme 4).

4). (2R*,5R,8S*)-2,8-diphenyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (6aa). To a stirred solution of (2R,4R)-4-(Hydroxymethyl)-2-phenylthiazolidine (550 mg, 2.82 mmol) in CH_2Cl_2 (30 mL) were added benzaldehyde (358 mg, 3.38 mmol) and *p*-TsOH (30 mg, 0.37 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified by chromatography (4:1, *n*-hexanes/AcOEt) to give **6aa** (450 mg, 99.9% de, 75 % yield) as a white solid: mp 85.2-85.4 $^\circ\text{C}$. IR (KBr) ν = 3085, 2857, 1491, 1381, 1092, 821 cm^{-1} ;

^1H NMR (CDCl_3), δ 2.91 (dd, J = 3.5, 11.4 Hz, 1 H), 3.12 (dd, J = 6.9, 11.4 Hz, 1 H), 3.80 (dd, J = 6.0, 8.3 Hz, 1 H), 4.19 - 4.24 (m, 1 H), 4.42 (dd, J = 6.5, 8.3 Hz, 1 H), 5.27 (s, 1 H_{NCHO}), 5.41 (s, 1 H_{SCHN}), 7.19-7.38 (m, 6 H), 7.44-7.46 (m, 2 H), 7.55-7.58 (m, 2 H); ^{13}C NMR (CDCl_3) δ 36.50, 67.18, 71.85, 73.54, 96.70, 126.76, S6

127.24, 127.75, 128.10, 128.41, 129.04, 139.18, 142.11; HRMS calculated for $C_{17}H_{17}NOS$ $[M-H]^+$: 283.1031, found: 283.1035. $[\alpha]_D$ -98.7° (22°C, CH_2Cl_2 , $c=1.02$).

(2*R,5*R*,8*S**)-2-(4-chlorophenyl)-8-phenyl-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (6ab).**

Prepared in 85.2% de, 80% yield, as a colourless oil analogous to the route described for **6aa**: IR (KBr) ν = 3085, 2932, 1599, 1491, 1105, 822 cm^{-1} ; 1H NMR ($CDCl_3$), δ 2.90 (dd, J = 3.5, 11.5 Hz, 1 H), 3.12 (dd, J = 6.9, 11.5 Hz, 1 H), 3.78 (dd, J = 6.0, 8.3 Hz, 1 H), 4.17 – 4.23 (m, 1 H), 4.40 (dd, J = 6.5, 8.3 Hz, 1 H), 5.24 (s, 1 H_{OCHN}), 5.37 (s, 1 H_{SCHN}), 7.20-7.34 (m, 5 H), 7.41-7.43 (m, 2 H), 7.48-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 36.42, 67.13, 71.87, 73.44, 96.05, 126.69, 127.38, 128.18, 128.62, 129.15, 134.84, 137.80, 141.86; HRMS calculated for $C_{17}H_{16}ClNOS$ $[M^+-H]$: 317.0641, found: 317.0644. $[\alpha]_D$ -67.8° (22°C, CH_2Cl_2 , $c=0.7$).

(2*R,5*R*,8*R**)-2-phenyl-8-(4-chlorophenyl)-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (6ba)**

Prepared in 98.7% ee, 95% yield, as a colourless oil analogous to the route described for **6aa**: IR (KBr) ν = 3087, 2859, 1489, 1383, 1090, 824 cm^{-1} ; 1H NMR ($CDCl_3$), δ 2.91 (dd, J = 3.5, 11.5 Hz, 2 H), 3.09 (dd, J = 6.6, 11.5 Hz, 2 H), 3.78 (dd, J = 6.2, 8.4 Hz, 2 H), 4.18 (dq, J = 3.5, 6.2, 6.5, 6.6 Hz, 1 H), 4.40 (dd, J = 6.5, 8.4 Hz, 2 H), 5.25 (s, 1 H_{OCHN}), 5.35 (s, 1 H_{SCHN}), 7.23-7.26 (m, 1 H), 7.33-7.39 (m, 6 H), 7.53-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 36.48, 67.11, 71.82, 72.87, 96.69, 127.68, 128.19, 128.45, 129.14, 132.99, 138.97, 140.64; HRMS calculated for $C_{17}H_{16}ClNOS$ $[M-H]^+$: 317.0641, found: 317.0644; $[\alpha]_D$ -122.6° (22°C, CH_2Cl_2 , $c=1.05$).

(2*R,5*R*,8*S**)-2,8-di-(4-chlorophenyl)-1-aza-3-oxa-7-thiabicyclo[3.3.0]octane (6bb)**

Prepared in 99.9% de, 60% yield, as a white solid analogous to the route described for **6aa**: mp 83.2 - 83.5 °C; IR (KBr) ν = 3054, 2934, 1489, 1375, 1088, 828 cm^{-1} ; 1H NMR ($CDCl_3$), δ 2.90 (dd, J = 3.4, 11.5 Hz, 1 H), 3.09 (dd, J = 6.8, 11.5 Hz, 1 H), 3.77 (dd, J = 6.1, 8.4 Hz, 1 H), 4.13–4.19 (m, 1 H), 4.40 (dd, J = 6.5, 8.4 Hz, 1 H), 5.22 (s, 1 H_{OCHN}), 5.31 (s, 1 H_{SCHN}), 7.24-7.27 (m, 2 H), 7.31-7.38 (m, 4 H), 7.46-7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 36.37, 71.79, 72.76, 96.04, 128.13, 128.26, 128.66, 129.08, 133.13, 134.93, 137.61, 140.39; HRMS calculated for $C_{17}H_{15}Cl_2NOS$ $[M-H]^+$: 351.0251, found: 351.0236. $[\alpha]_D$ -122.7° (22°C, CH_2Cl_2 , $c=1.00$).

Typical procedure for thiazolidine-oxazolidine exchange (Scheme 6). A mixture of compound **6aa** (100 mg, 0.36 mmol), *p*-Cl-benzaldehyde (50 mg, 0.36 mmol) in CH_2Cl_2 (35.5 mL) and *p*-TsOH (10 mg, 0.13 mmol) was

stirred at rt for 2 d. The reaction mixture was poured into water, the pH adjusted to pH 7 and extracted with CH₂Cl₂ (3x30 mL). The organic layers were dried, filtered and solvent was removed under reduced pressure. The residue was analyzed by ¹H NMR to determine the product ratio: **6aa** (55 %), **6ab** (31 %), and **5a** (14%) and purified by chromatography on SiO₂ (AcOEt/*n*-hexanes 1:9) to give a mixture of **6aa** + **6ab** (91 mg, 85 %) and **5a** (10 mg, 14 %).

Compounds were identified by running pure samples of compounds **6aa**, **6ab**, **6ba** and **5b** by HPLC in a CHIRALCEL OD column (0.46cm ID x 25 cm) using an isocratic system isopropanol/*n*-Hexanes (10:90), λ = 210 or 190 nm. They were identified in the following order: **5b**: *t*_r = 3.3 min, **6ab**: *t*_r = 5.5 min; **6aa**: *t*_r = 6.5 min; **6ba**: *t*_r = 6.8 min.

Cecilia CS222

Cecilia CS242

Cecilia CS242

Cec11a CS 235

7.56
7.46
7.44
7.36
7.34
7.29
7.25
7.21
7.19

5.41
5.27

4.44
4.42
4.42
4.40
4.25
4.19

3.82
3.80
3.79
3.78

3.14
3.12
3.11
3.10
2.93
2.92
2.90
2.89

0.00

1.95
0.89
1.91
5.62

0.98
0.99

1.00
1.00

1.00

0.72
1.01

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

Graciela GML9 / E3- /
gm.1120

6aa

Cecilia GM 197 bis NOE d=5.41ppm

7.46
7.45
7.44
7.43
7.31
7.26
7.21

baa

Cecilia GM 197 bis NOE d=5.27ppm

6aa

Cecilia CS 234

7.41
7.34
7.33
7.33
7.31
7.31
7.29
7.29
7.27
7.25
7.24
7.22

5.41
5.37
5.27
5.24

4.42
4.40
4.39
4.38
4.23
4.21
4.21
4.20
4.19
4.18
3.80
3.79
3.78
3.77

3.14
3.12
3.11
3.09
2.92
2.91
2.89
2.88

1.55

0.00

CS.1182

wdd

Cecilia CS232 F10

Cecilia CS 232
CS.1181

Cecilia CS 233

Cecilia CS 233
cs.1180

140.39
137.61
134.93
133.13
129.08
128.66
128.26
128.13

96.04

77.32
77.00
76.68

72.76
71.79

67.04

36.37

140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 ppm

a) ^1H NMR acetal signals for aminoalcohol **5a**; b) ^1H NMR signals for compound *anti*-**6ab**, showing traces of its diastereomer; c) ^1H NMR acetal signals for bicycle **6aa**; d) ^1H NMR acetal signals for the exchange reaction of **6aa** and **1b** at 10 mM in CH_2Cl_2 in the presence of p-TsOH.

==== Shimadzu LCsolution UV

<UV Spectrum Index>

File Name : C:\LabSolutions\Data\Farmacial\Biciclo H-Cl.lcd

==== Shimadzu LCsolution

UV Spectrum

<UV Spectrum Index>

File Name : C:\LabSolutions\Data\Farmacial\Biciclo H-H.lcd

==== Shimadzu LCsolution UV Spectrum

HPLC chromatogram of the equilibrated mixture of compound 6aa, aldehyde *p*-ClPhCHO at [10mM] each, 2d, r.t. at 210 nm

==== Shimadzu LCsolution UV Spectrum