Diastereoselective functionalizations of enecarbamates derived from pipecolic acid towards 5-guanidinopipecolates as arginine mimetics.

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Preparation of substrates 3

rac-**Dimethyl 3,4-dihydropyridine-1,2(*2H*)-dicarboxylate** *rac*-**3a.**

Into an undivided beaker type cell with cooling mantle equipped with graphite electrodes plates (15 cm^2), was introduced **1a** (10 g, 49.8 mmol), tetrabutylammonium tetrafluoroborate (2 g, 6.1 mmol) and MeOH (80 mL). The mixture was cooled down to – 10 °C and then electrolyzed under a constant voltage of 12 V (initial current 0.55-0.64 A). After, 2.5–3 F/mol, according to monitoring by GC, the mixture was concentrated under reduced pressure then taken up in DCM (100 mL), washed with water (2×100 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To the crude product (neat), was added NH_4Cl (15.8 g, 0.29 mol) and the mixture was heated for 5 h at 80 °C under reduced pressure (10 mm Hg). Et_2O (100 mL) was added; after filtration through a pad of Celite® the white precipitate was washed with Et_2O (100 mL) and the filtrate was concentrated in vacuo. Purification by column chromatography (cyclohexane/EtOAc 8:2, and up to 1:1) afforded enecarbamate **3a** (8.58 g, 73% yield) as a colourless oil: R_f = 0.49 (EtOAc/cyclohexane 1:1); ν_{max}(neat)/cm^{-1} 2955, 2846, 1747, 1706, 1656, 1441, 1349, 1203; δ_H (250 MHz, $CDCl_3$; Me_4Si) 6.91 (0.4 H, d, *J* 8.5, 6-H), 6.78 (0.6 H, d, *J* 8.5, 6-H), 4.97–4.79 (2 H, m, 2-H, 5-H), 3.77 (1.8 H, s, CO_2CH_3), 3.71 (4.2 H, s, CO_2Me and NCO_2CH_3), 2.38-2.29 (1 H, m, 4-H), 2.02-1.86 (3 H, m, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 170.9, 169.9 ($\underline{C}O_2CH_3$), 153.5 ($N\underline{C}O_2CH_3$), 124.2, 123.8 (CH-6), 105.0, 104.8 (CH-5), 53.6, 53.3, 52.8, 52.0 (CH-2, $CO_2\underline{C}H_3$, $NCO_2\underline{C}H_3$), 23.2, 23.1 (CH_2-4), 18.1, 17.9 (CH_2-3).

rac-**1-*tert*-Butyl 2-methyl 3,4-dihydropyridine-1,2(*2H*)-dicarboxylate** *rac*-**3b.**

After electrolysis of **1b** (9.86 g, 40.57 mmol) in presence of tetrabutylammonium tetrafluoroborate (1.79 g, 5.43 mmol) and CH_3OH (70 mL), as above, the crude product resulting from workup of electromethoxylation was dissolved in toluene (120 mL) and solid ammonium chloride (3.0 g, 56.07 mmol) was added. The resulting heterogeneous mixture was heated at reflux for 3 h. After filtration over a pad of Celite® and washing with Et_2O, the filtrate was concentrated in vacuo and the residue purified by column chromatography (cyclohexane/EtOAc 85:15). Enecarbamate **3b** was isolated as a colourless oil (9.05 g, 93%

yield): R_f = 0.52 (EtOAc/cyclohexane 1:1); ν_{max}(neat)/cm^{-1} 2977, 1752, 1707, 1655, 1352, 1166, 1069, 770; δ_H (250 MHz, $CDCl_3$; Me_4Si) 6.88 (0.5 H, d, *J* 8.3, 6-H), 6.76 (0.5 H, d, *J* 8.3, 6-H), 5.05–4.60 (2 H, m, 2-H, 5-H), 3.70 (3 H, s, CO_2CH_3), 2.35-2.15 (1 H, m, 4-H), 2.05-1.75 (3 H, m, 3-H, 4-H), 1.48, 1.43 (9 H, 2×s, *t*-Bu); δ_C (63 MHz, $CDCl_3$) 171.8, 171.4 ($\underline{C}O_2CH_3$), 152.3, 152.2 ($\underline{C}O_2$*t*-Bu), 124.8, 124.3 (CH-6), 104.5, 104.0 (CH-5), 81.2, 81.0 ($\underline{C}Me_3$), 54.3, 53.0 (CH-2), 52.2 ($CO_2\underline{C}H_3$), 28.1, 28.0 ($C\underline{Me_3}$), 23.5, 23.4 (CH_2-4), 18.4, 18.2 (CH_2-3).

(5*R,6*S**,8a*S**)-6-azido-5-methoxy-tetrahydro-*1H*-oxazolo[3,4-a]pyridin-3(*5H*)-one** *cis-* **4c.**

From enecarbamate **3c** (191 mg, 1.38 mmol), NaN_3 (134 mg, 2.07 mmol) and CAN (2.27 g, 4.14 mmol), as described above. Flash column chromatography (cyclohexane/EtOAc 7:3) afforded 256 mg of a *cis/trans* (80:20) mixture of 5-azido compounds **4c** (83%), from which the major isomer could be isolated. R_f = 0.29 (cyclohexane/EtOAc 6:4); ν_{max}(neat)/cm^{-1} 2946, 2095, 1741, 1402, 1360, 1236, 1196, 1167, 1088, 1030, 995; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.82 (1 H, br s, 5-H), 4.47 (1 H, t, *J* 8.0 and *J* 8.0, CH_2O), 3.99-3.75 (3 H, m, 8*a*-H, 6-H, CH_2O), 3.32 (3 H, s, OCH_3), 2.10-1.55 (4 H, m, 7-H, 8-H); δ_C (63 MHz, $CDCl_3$) 157.3 (NCO_2), 82.0 (CH-5), 68.9 (CH_2O), 57.3 (CH-6), 55.7 (OCH_3), 49.3 (CH-8*a*), 24.4 (CH_2-7), 22.4 (CH_2-8); MS (ESI): *m/z* = 230 $[M+NH_4]^+$ 100%.

6-Azido-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine 5c

Reduction of the *cis/trans* (70:30) mixture of azidomethoxylation compound **4c** (200 mg, 0.94 mmol) with Et_3SiH (110 μL, 1.33 mmol) and $BF_3.OEt_2$ (170 μL, 1.35 mmol) afforded a *trans/cis* (70:30) mixture of azido compounds **5c**. Flash column chromatography (EtOAc/cyclohexane 90:10) afforded pure *cis*-**5c** (94 mg, 55%) and *trans*-**5c** azido (35 mg, 20%).

(6*S,8a*S**)-6-Azido-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine** *cis*-**5c**.

R_f = 0.28 (EtOAc/Cyclohexane 90:10); ν_{max}(neat)/cm^{-1} 2928, 2089, 1743, 1424, 1332, 1265, 1152, 1097, 1060, 959; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.41 (1H, dd, *J* 8.5 and *J* 8.5, CH_2O), 4.01-3.79 (3 H, m, 5-H, 6-H, CH_2O), 3.76-3.61 (1 H, m, 8*a*-H), 3.68–3.55 (1 H, m, 8*a*-H), 3.04 (1 H, dd, *J* 14.0 and 2.8, 5-H), 2.15–1.95 (1 H, m, 7-H), 1.83-1.56 (3 H, 7-H, 8-H); δ_C (63 MHz, $CDCl_3$) 157.3 (NCO_2), 68.0 (CH_2O), 54.7 (CH-6), 53.5 (CH-8*a*), 44.2 (CH_2-5), 26.4 (CH_2-7), 24.8 (CH_2-8); MS (ESI): *m/z* = 183 $[M+H]^+$ 100%.

(6*R,8a*S**)-6-Azido-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine** *trans*-**5c**.

R_f = 0.41 (EtOAc/Cyclohexane 90:10); ν_{max}(neat)/cm^{-1} 2923, 2099, 1745, 1424, 1317, 1251, 1164, 1125, 1063, 966; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.38 (1H, dd, *J* 8.0 and *J* 8.0, CH_2O), 4.02 (1 H, ddd, *J* 12.9, 5.4 and 2.0, 5-H), 3.88 (1 H, dd, *J* 8.0 and *J* 8.0, CH_2O), 3.70-3.50 (1 H, m, 8*a*-H), 3.46-3.25 (1H, m, 6-H), 2.65(1 H, dd, *J* 13.0 and 11.0, 5-H), 2.28-2.06 (1 H, m, 7-H), 2.03-1.80 (1H, m, 8-H), 1.51-1.37 (2 H, 7-H, 8-H); δ_C (63 MHz, $CDCl_3$) 156.7 (NCO_2), 67.8 (CH_2O), 55.7 (CH-6), 53.4 (CH-8*a*), 45.2(CH-5), 29.1, 28.9 (CH_2-7, CH_2-8).

(2*S,5*S**)-5-Azido-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid *cis*-5’b.**

To a solution of the azido ester *cis*-**5b** (869 mg, 3.06 mmol) in MeOH (23 mL) was added 0.67 M aqueous LiOH (11.5 mL) and the mixture was stirred at r.t. for 16 h. The solution was concentrated in vacuo. Water (15 mL) was added and the mixture was extracted with Et_2O (2×40 mL). The aqueous phase was acidified with 10% citric acid (13 mL) and extracted with DCM (3×40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to afford the azido acid compound *cis*-**5’b** as a colourless oil (816 mg, 99%). ν_{max}(neat)/cm^{-1} 2976, 2098, 1736, 1695, 1473, 1408, 1392, 1367, 1325, 1245, 1147, 1052, 1005; δ_H (250 MHz, $CDCl_3$; Me_4Si) 10.44 (1 H, s, CO_2H), 5.05–4.65 (1 H, m, 2-H), 4.40–3.95 (1 H, m, 6-H), 3.45–3.20 (1 H, m, 5-H), 2.92–2.56 (1 H, m, 6-H), 2.45–2.23 (1 H, m, 3-H), 2.20–1.93 (1 H, m, 4-H), 1.90–1.60 (1 H, m, 3-H), 1.55–1.20 (10 H, m, CMe_3, 4-H); δ_C (63 MHz, $CDCl_3$) 175.3, 175.2 (CO_2H), 155.3, 155.0 (N$\underline{C}O_2$*t*Bu), 81.2 ($\underline{C}Me_3$), 56.1 (CH-5), 53.4, 52.3 (CH-2), 45.6, 44.5 (CH_2-6), 28.0 (C$\underline{Me_3}$), 26.6 (CH_2-4), 24.9, 24.7 (CH_2-3); MS (ESI): *m/z* = 171 $[M-C_5H_8O_2+H]^+$ 100%.

(2*S,5*R**)-5-Azido-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid *trans*-5’b.**

Saponification of *trans*-azido ester **5b** (147 mg, 0.52 mmol), performed as above, afforded the azido acid *trans*-**5’b** as a white solid (135 mg, 96%). ν_{max}(neat)/cm^{-1} 2971, 2113, 1741, 1620, 1475, 1436, 1392, 1372, 1314, 1263, 1248, 1204, 1168, 1147, 1132, 1031, 1013; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.15-4.70 (1 H, m, 2-H), 4.27–4.00 (1 H, m, 6-H), 3.90–3.65 (1 H, m, 5-H), 3.40–3.00 (1 H, m, 6-H), 2.20–1.96 (2 H, m, 3-H), 1.94–1.30 (11 H, m, CMe_3, 4-H); δ_C (63 MHz, $CDCl_3$) 177.3 (CO_2H), 155.9 ($\underline{C}O_2$-*t*-Bu), 81.4 ($\underline{C}Me_3$), 55.1 (CH-5), 54.3, 53.0 (CH-2), 44.4, 43.8 (CH_2-6), 28.4 (C$\underline{Me_3}$), 25.1 (CH_2-4), 21.0 (CH_2-3); MS (ESI): *m/z* = 171 $[M-C_5H_8O_2+H]^+$ 100%.

Halogenomethoxylation of 3

To a 0.1 M solution of enecarbamate **3** in MeOH , was added a solution of NBS (1equiv.) or NIS (1 equiv.) in THF, at – 70 °C. After stirring for 90 min at – 70 °C; the temperature was raised up to r.t. and the mixture was concentrated in vacuo, and then subjected to purification without workup.

(2*S,5*R**,6*S**)-dimethyl 5-bromo-6-methoxypiperidine-1,2-dicarboxylate 6a.**

Prepared according to the above procedure, starting from enecarbamate **3a** (1.04 g, 5.22 mmol) in MeOH (50 mL), and NBS (936 mg, 5.26 mmol) in THF (15 mL). Flash column chromatography (EtOAc/cyclohexane 8:2) afforded **6a** (1.55 g, 89%) as a 96:4 *trans/cis* mixture, from which the major 2,5-*tarns*; 2,6-*cis* isomer of **6a** could be isolated as a colourless powder: mp 64–66 °C; R_f = 0.41 (cyclohexane/EtOAc 6:4); ν_{max}(neat)/cm^{-1} 2954, 1739, 1706, 1440; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.51 (0.4 H, br s, 6-H), 5.33 (0.6 H, br s, 6-H), 4.94 (0.6 H, br s, 2-H), 4.75 (0.4 H, br s, 2-H), 4.26 (1 H, br s, 5-H), 3.79 (3 H, s, CO_2CH_3), 3.70 (3 H, s, NCO_2CH_3), 3.33 (1.2 H, s, 6-OCH_3), 3.30 (1.8 H, s, 6-OCH_3), 2.45-2.33 (1 H, m, 4-H), 2.18–2.07 (2 H, m, 3-H); 1.82–1.75 (1 H, m, 4-H); δ_C (63 MHz, C_6D_6) 171.4 ($\underline{C}O_2CH_3$), 157.0, 156.4 ($N\underline{C}O_2CH_3$), 86.0, 85.5 (CH-6), 56.8, 56.1 (6-OCH_3), 52.9 ($CO_2\underline{C}H_3$), 51.5, 51.4 (CH-2), 50.9, 50.4 ($NCO_2\underline{C}H_3$), 49.8, 49.4 (CH-5), 23.9, 23.8 (CH_2-4), 19.7, 19.5 (CH_2-3).

(2*S,5*R**,6*S**)-dimethyl 5-iodo-6-methoxypiperidine-1,2-dicarboxylate 6'a.**

Prepared according to the above procedure, starting from enecarbamate **3a** (500 mg, 2.51 mmol) in MeOH (25 mL), and NIS (565 mg, 2.51 mmol) in THF (8 mL). Flash column chromatography (EtOAc/cyclohexane 8:2) afforded a 95:5 diastereomeric mixture of 5-iodo-6-methoxy derivative **6'a** (600 mg, 67%), from which the title compound (major diastereomer) could be isolated. R_f = 0.33 (cyclohexane/EtOAc 7:3); δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.58 (0.4 H, br s, 6-H), 5.41 (0.6 H, br s, 6-H), 4.95 (0.6 H, br s, 2-H), 4.75 (0.4 H, br s, 2-H), 4.45 (1 H, br s, 5-H), 3.80 (3H, br s, CO_2CH_3), 3.69 (3 H, br s, NCO_2CH_3), 3.32 (1.2 H, s, OCH_3), 3.28 (1.8 H, s, OCH_3), 2.45-2.05 (3 H, m, 3-H, 4-H), 1.85-1.60 (1 H, m, 3-H); δ_C (63 MHz, $CDCl_3$) 171.8 ($\underline{C}O_2CH_3$), 157.1, 156.6 (NCO_2CH_3), 87.1, 86.4 (CH-6), 56.9, 56.5 (OCH_3), 53.5, 52.8, 52.1 ($CO_2\underline{C}H_3$), 50.8, 50.2 (CH-2), 29.4, 29.0 (CH-5), 24.8 (CH_2-4), 21.3, 21.0 (CH_2-3).

(5*R,6*S**,8a*S**)-6-Iodo-5-methoxy-tetrahydro-1*H*-oxazolo[3,4-*a*]pyridin-3(5*H*)-one 6'c.**

Prepared according to the above procedure, starting from enecarbamate **3c** (153 mg, 1.10 mmol) in MeOH (8 mL) and NIS (248 mg, 1.10 mmol) in THF (2.2 mL). Flash column chromatography (EtOAc/cyclohexane 5:5) afforded a *cis/trans* mixture (>95:5) of 5-iodo-6-methoxy **6'c** as colourless oil (299 mg, 92%) from which the title compound (major diastereomer) could be obtained. R_f = 0.27 (cyclohexane/EtOAc 5:5); δ_H (250 MHz, $CDCl_3$;

Me_4Si) 5.16 (1 H, br s, 5-H), 4.52 (1 H, dd, *J* 7.7 and *J* 7.7, CH_2O), 4.43 (1 H, br s, 6-H), 4.07–3.84 (2 H, m, 8*a*-H, CH_2O), 3.33 (3 H, s, OCH_3), 2.25–1.65 (4 H, m, 8-H, 7-H); δ_C (63 MHz, $CDCl_3$) 157.4 (NCO_2), 85.6 (CH-5), 69.1 (CH_2O), 55.8 (OCH_3), 49.5 (CH-8a), 27.2 (CH_2), 26.8 (CH-6), 26.6 (CH_2).

(2*S,5*R**)-Dimethyl *trans*-5-bromopiperidine-1,2-dicarboxylate** *trans*-**7a.**

To a solution of compound **6a** (0.45 g, 1.45 mmol as a 96/4 *trans/cis* mixture) and Et_3SiH (230 µL, 1.45 mmol) in DCM (19 mL), was added $BF_3.OEt_2$ (367 µL, 2.9 mmol), at – 80 °C and the reaction mixture was stirred for an additional 15 min at – 80°C. The reaction mixture was kept under stirring and the temperature was left to rise to 10°C, then a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the resulting mixture worked up as described above in the preparation of 5-azido derivatives **5**. Flash column chromatography (EtOAc/cyclohexane 6:4) afforded a *trans/cis* mixture (95:5) of 5-bromo derivative **7a** (345 mg, 85%). ν_{max}(neat)/cm^{-1} 2954, 2849, 1738, 1699, 1445, 1365, 1247, 1206, 1151, 1115, 1015, 954, 810, 785, 768; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.06–4.80 (1 H, m, 2-H), 4.48–4.15 (2 H, m, 5-H, 6-H), 3.78–3.60 (6 H, m, CO_2CH_3, NCO_2CH_3), 3.54–3.35 (1 H, m, 6-H), 2.41–2.25 (1 H, m, 3-H), 2.13–1.95 (2 H, m, 3-H, 4-H), 1.85–1.69 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 170.9 ($\underline{C}O_2CH_3$), 156.2, 155.8 ($N\underline{C}O_2CH_3$), 53.2, 52.9 (CH-2), 52.5, 51.8 ($CO_2\underline{C}H_3$), 48.1 (C-6), 47.9 (C-5), 28.7 (C-4), 20.7 (C-3)

(2*S,5*S**)-Dimethyl *trans*-5-bromopiperidine-1,2-dicarboxylate** *cis*-**7a.**

Could also be obtained in 82% yield from alcohol *trans*-**8a** as follows: to a solution of *trans*-**8a** (172 mg, 0.79 mmol) in THF (13 mL), were added carbon tetrabromide (1.3 g, 3.95 mmol), tetrabutylammonium fluoride (27 mg, 0.08 mmol) and, portionwise triphenylphosphine (1.03 g, 3.95 mmol), at 0 °C. The mixture was stirred at r.t. for 16 h, filtered through a Celite pad and washed with DCM. The filtrate was concentrated in vacuo. Purification by flash column chromatography afforded pure *cis*-**7a** as a colourless oil (180 mg, 82%); ν_{max}(neat)/cm^{-1} 2955, 1740, 1702, 1443, 1404, 1310, 1206, 1150, 1121, 1004, 769, 727; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.95–4.78 (1 H, m, 2-H), 4.50–4.28 (1 H, m, 6-H), 3.90–3.60 (m, 7 H, 5-H, CO_2CH_3, NCO_2CH_3), 3.23–3.01 (1 H, m, 6-H), 2.35–2.15 (2 H, m, 3-H, 4-H), 1.90–1.59 (2 H, m, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 170.9 ($\underline{C}O_2CH_3$), 155.8, 155.5 ($N\underline{C}O_2CH_3$), 53.3 (CH-2), 53.1 ($CO_2\underline{C}H_3$), 52.9 (CH-2), 52.5 ($CO_2\underline{C}H_3$), 49.0, 48.7 (CH_2-6), 44.5 (CH-5), 32.5 (CH_2-4), 28.0, 27.8 (CH_2-3).

(*6R*,8aS)-6-hydroxytetrahydro-*1H*-oxazolo[3,4-a]pyridin-3(*5H*)-one** *trans*-**8c.**

Oxidative hydroboration of **3c** (213 mg, 1.53 mmol) led to **8c** (84 mg, 35% yield) as an approximately 1/1 mixture of C-5 epimers along with compound **1c** (25 mg, 15%). Pure *trans*-**8c** was obtained by transesterification of the corresponding acetate *trans*-**11c** with catalytic amount of potassium carbonate in methanol.

R_f = 0.29 (EtOAc/MeOH 95:5); ν_{max}(neat)/cm^{-1} 3352, 2931, 1742, 1435, 1253, 1071; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.39 (1 H, t, *J* 8.5 t, CH_2O), 4.00 (1 H, ddd, *J* 12.8**,** 5.4 and 1.8, 6-H), 3.88 (1 H, t, *J* 8.5, CH_2O), 3.72–3.54 (2 H, m, 2-H, 5-H), 2.63 (1 H, dd, *J* 12.8, and 10.3, 6-H), 2.56 (1 H, br s, OH), 2.18–2.06 (1 H, m), 1.94–1.83 (1 H, m), 1.47-1.37 (2 H, m); δ_C (63 MHz, $CDCl_3$) 157.0 (N$\underline{C}O_2$), 67.7 ($\underline{C}H_2O$), 65.7 (CH-6), 53.5 (CH-8a), 47.7 (CH_2-5), 31.9 (CH_2-7), 29.1 (CH_2-8).

rac **-Dihydro-*1H*-oxazolo[3,4-a]pyridine-3,6-dione 12c.**

Obtained by hydroboration of enecarbamate **3c** (406 mg, 2.92 mmol) with $BH_3.SMe_2$ (2 M in THF, 1.46 mL, 2.92 mmol) in Et_2O (9 mL); and then oxidation with IBX (3.2 g, 11.68 mmol) in CH_3CN (40 mL), according to the procedure described above. Flash column chromatography (EtOAc/MeOH 97:3) afforded ketone **12c** as a yellow oil (300 mg, 66%): R_f = 0.28 (EtOAc); ν_{max}(neat)/cm^{-1} 2925, 2854, 1717, 1648, 1430, 1247; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.59-4.50 (1 H, m, CH_2O), 4.31 (1 H, d, *J* 18.1, 5-H), 4.12–3.98 (2 H, m, 8a-H, CH_2O), 3.65 (1 H, d, *J* 18.1, 5-H), 2.68 (1 H, dt, *J* 16.8 and 4.0, 7-H), 2.53–2.38 (1 H, m, 7-H), 2.23–2.12 (1 H, m, 8-H), 2.03–1.84 (1 H, m, 8-H); δ_C (63 MHz, $CDCl_3$) 202.4 (C-5), 156.2 (N$\underline{C}O_2$), 67.2 (CH_2O), 51.4 (CH-8a), 50.9 (CH-5), 36.8 (CH_2-7), 27.7 (CH_2-8).

General methods for preparation of 5-acetoxypipecolate derivatives 11

Method A (*with OsO_4/Me_3NO*): to a *ca* 0.5 M solution of enecarbamate **3** in a 1:1 mixture of *t*-BuOH/H_2O, were added trimethylamine *N*-oxide (1.1 equiv.) and 1% aq. solution of OsO_4 (0.5 mL per mmol), and the reaction mixture was stirred at r.t. for 30 min to 3 h, as monitored by TLC.[24c] Water (10 mL) was added before introduction of solid Na_2SO_3 (3 equiv.) at 0 °C. After stirring for additional 10 min, the mixture was extracted with EtOAc (3 × 20 mL), dried over $MgSO_4$ and concentrated in vacuo. To the residue dissolved in DCM, were added Ac_2O (6-8 equiv.), DMAP (0.3 equiv.) and triethylamine (6–8 equiv.) then the mixture was stirred at r.t for 1–3 h. The reaction mixture was treated with a saturated aqueous solution of ammonium chloride, and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude diacetate **9’** was dissolved in DCM, and then boron trifluoride etherate and triethylsilane were added successively at – 80 °C. The reaction temperature was allowed to warm to r.t. A saturated aqueous solution of $NaHCO_3$

was added, and the organic layer was extracted with DCM, dried over $MgSO_4$, and concentrated in vacuo. Products were purified by flash column chromatography (unless otherwise indicated).

Method B (With Oxone®in H_2O): to a *ca*. 0.5 M solution of enecarbamate **3** in acetone/water (v/v: 4/1), were added solid $NaHCO_3$ (1.6 equiv.) and Oxone® (3 equiv.) The mixture was stirred at r.t. until total conversion of substrate **3**, according to TLC monitoring, then filtered and concentrated in vacuo to afford an oily dihydroxylated product. Subsequent acetylation and reduction were performed according to the procedure described above in method A.

Method C (with Oxone® in MeOH): to a *ca*. 0.07 M solution of enecarbamate **3** in methanol, were added $NaHCO_3$ (2 equiv.) and Oxone® (3 equiv.). The mixture was stirred at r.t. for 4 days (for 1 mmol scale). After filtration of the heterogeneous mixture, the solid residue was washed with DCM, and the filtrate was concentrated in vacuo. The oily residue was submitted to acetylation and reduction, as described above in method A, to afford compound **11** after flash column chromatography purification.

(2*S,5*R**)-Dimethyl *trans*-5-acetoxypiperidine-1,2-dicarboxylate** *trans*-**11a.**

According to method A: From **3a** (266 mg, 1.34 mmol); the two first steps (dihydroxylation/acetylation) afforded, after purification by flash column chromatography (EtOAc/cyclohexane1:1), a diastereomeric mixture of diacetate **9'a** as a colourless oil (316 mg, 75% for 2 steps). The final reduction step afforded, after flash chromatography (cyclohexane/EtOAc 7:3), a *trans/cis* (92:8) mixture of acetate **11a** (240 mg, 69% overall) as a colourless oil.

According to method B: From **3a** (281 mg, 1.41 mmol); diacetate **9'a** was isolated (by flash column chromatography 5EtOAc/cyclohexane1:1) as a colourless oil (300 mg, 67% for 2 steps). The reduction step afforded, after purification by flash column chromatography a *trans/cis* (85:15) mixture of acetate **11a** (200 mg, 55%) as colourless oil.

According to method C: From **3a** (200 mg, 1.0 mmol); acetate **11a** was obtained as a *trans/cis* (55:45) mixture (151 mg, 58% for 3 steps) as colourless oil.

R_f = 0.30 (EtOAc/Cyclohexane 1:1); ν_{max}(neat)/cm^{-1} 2956, 1734, 1699, 1444, 1369, 1226, 1120, 1021, 770; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.05–4.87 (2 H, m, 2-H, 5-H), 4.25–4.09 (1 H, m, 6-H), 3.73 (3 H, s, CO_2CH_3), 3.70 (3 H, s, CO_2CH_3), 3.27–3.12 (1 H, m, 6-H), 2.20–1.70 (5 H, m including s, OAc, 3-H, 4-H), 1.69–1.40 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 171.5, 170.2 ($\underline{C}O_2CH_3$, OAc), 157.0, 156.4 ($N\underline{C}O_2CH_3$), 66.1 (CH-2), 53.8, 53.5 (CH-5), 52.8, 52.1

($CO_2\underline{C}H_3$), 44.5 (CH_2-6), 24.5 (CH_2-4), 20.9 ($OCO_2\underline{C}H_3$), 20.8 (CH_2-3); MS (ESI): m/z = 260 $[M+H]^+$ 100%.

(2*S,5*R**)-1-*tert*-Butyl 2-methyl *trans*-5-acetoxypiperidine-1,2-dicarboxylate** *trans*-**11b.**

According to method B: **3b** (500 mg, 2.07 mmol) lead to a *trans/cis* (86:14) mixture (277 mg, 44%) of acetate **11b** which was isolated as colourless oil.

R_f = 0.29 (Cyclohexane/EtOAc 7:3); ν_{max}(neat)/cm^{-1} 2972, 2953, 1738, 1696, 1448, 1416, 1364, 1337, 1231, 1199, 1172, 1149, 1120, 1021; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.12–4.60 (2 H, m, 2-H, 5-H), 4.25–4.03 (1 H, m, 6-H), 3.72 (3 H, s, CO_2CH_3), 3.26–2.94 (1 H, m, 6-H), 2.13–1.93 (4 H, m, OAc, 3-H), 1.91–1.73 (1 H, m, 4-H), 1.52–1.35 (11 H, m, *t*-Bu, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 171.8, 170.0 ($\underline{C}O_2CH_3$, OAc), 155.4 ($N\underline{C}O_2$-*t*-Bu*t*), 80.1 ($\underline{C}Me_3$), 66.4, 66.2 (CH-5), 54.3, 52.8 (CH-2), 52.0 ($CO_2\underline{C}H_3$), 44.6, 43.9 (CH_2-6), 28.1 ($C\underline{Me_3}$), 24.6, 24.4 (CH_2-4), 20.9 ($H_3\underline{C}$-CO_2-), 20.8 (CH_2-3).

6-acetoxy-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine 11c.

According to method A: Enecarbamate **3c** (400 mg, 2.88 mmol) afforded, in three steps, after final flash column chromatography (cyclohexane/EtOAc 7:3) a *trans/cis* (70:30) mixture of acetylated compound **11c** (344 mg, 60%) as a colourless oil, from which pure *trans* diastereomer could be isolated.

According to method B: Enecarbamate **3c** (200 mg, 1.44 mmol) afforded a *cis/ trans* (63:37) mixture of acetylated compound **11c** (215 mg, 75%) as a colourless oil from which pure *cis* diastereomer could be isolated.

According to method C: Enecarbamate **3c** (200 mg, 1.44 mmol) afforded a *cis/ trans* (70:30) mixture of acetylated compound **11c** (240 mg, 84%) as a colourless oil from which pure *cis* diastereomer could be isolated.

(6*R,8a*S**)-6-acetoxy-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine** *trans*-**11c**: R_f = 0.34 (EtOAc/Cyclohexane 8:2); ν_{max}(neat)/cm^{-1} 2962, 2871, 1732, 1438, 1251, 1237, 1054, 751; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.76–4.60 (1 H, m, 6-H), 4.41 (1H, dd, J 8.6 and J 8.6, CH_2O), 4.06 (1 H, ddd, J 12.5, 5.5 and 1.5, 5-H), 3.89 (1 H, dd, J 8.6 and 8.6, CH_2O), 3.68–3.55 (1 H, m, 8*a*-H), 2.73 (1 H, dd, J 12.5 and 10.6, 5-H), 2.27–2.14 (1 H, m), 2.03 (3 H, s, OAc), 1.98-1.88 (1 H, m), 1.53-1.39 (2 H, m); δ_C (63 MHz, $CDCl_3$) 169.8 (OAc), 156.5 (NCO_2), 67.7 (CH_2O), 67.3 (CH-6), 53.4 (CH-8*a*), 44.4 (CH_2-5), 28.5 (CH_2-7), 28.4 (CH_2-8), 20.9 (CH_3); MS (ESI): m/z = 217 $[M+NH_4]^+$ 100%.

(6*S,8a*S**)-6-acetoxy-3-oxohexahydro-*1H*-oxazolo[3,4-a]pyridine** *cis*-**11c**: R_f = 0.22 (EtOAc/Cyclohexane 8:2); ν_{max}(neat)/cm^{-1} 2927, 1722, 1435, 1254, 1228, 1043, 1019, 758;

δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.98–4.94 (1 H, m, 6-H), 4.41 (1 H, dd, *J* 8.3 and 8.3, CH_2O), 4.04–3.92 (2 H, m, CH_2O, 5-H), 3.78–3.66 (1 H, m, 8*a*-H), 3.03 (1 H, dd, *J* 14.6 and 2.1, 5-H), 2.15–1.99 (4 H, m including s for OAc), 1.89–1.60 (3 H, m); δ_C (63 MHz, $CDCl_3$) 170.3 (OAc), 157.5 (NCO_2), 67.8 (CH_2O), 65.6 (CH-6), 53.6 (CH-8*a*), 44.5 (CH_2-5), 26.5 (CH_2-7), 24.4 (CH_2-8), 20.9 (CH_3); MS (ESI): *m/z* = 217 $[M+NH_4]^+$ 100%.

Preparation of sulfonates 13 and 14

*Tosylation***:** to a solution of alcohol **8** in pyridine were added tosyl chloride (2 equiv.) and DMAP (1 equiv.) at r.t. and the reaction mixture was stirred at 70 °C for 9 h. After concentration in vacuo, the mixture was washed with a saturated solution of NH_4Cl and the organic layer was extracted with DCM. The combined organic layers were washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo then submitted to purification by column chromatography.

Mesylation: to a solution of alcohol **8** in DCM, were added Et_3N (2 equiv.) and mesyl chloride (1.5 equiv.), at 0 °C. The reaction mixture was stirred at r.t. for 2 h and then worked up as for tosylation.

(2*S,5*S**)-Dimethyl 5-(methylsulfonyloxy)piperidine-1,2-dicarboxylate *cis*-13a.**

Mesylation of alcohol *cis*-**8a** (1.9 g, 8.76 mmol) afforded after purification by flash column chromatography (cyclohexane/EtOAc 1:1), mesylate *cis*-**13a** as a colourless oil (2.1 g, 81%). R_f = 0.23 (EtOAc/cyclohexane 1:1); δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.95–4.66 (1 H, m, 2-H), 4.64–4.20 (2 H, m, 5-H, 6-H), 3.78–3.65 (6 H, m, CO_2CH_3), 3.10–2.85 (4 H, m, 6-H, CH_3SO_2), 2.45–2.05 (2 H, m, 3-H, 4-H), 1.90–1.66 (1 H, m, 3-H), 1.64–1.40 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 170.8 ($\underline{C}O_2CH_3$), 156.0, 155.8 ($N\underline{C}O_2CH_3$), 74.5 (CH-5), 53.5, 53.1, 52.3 (CH-2, $NCO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 45.2, 44.8 (CH_2-6), 38.4 (CH_3SO_2), 27.8 (CH_2-4), 24.8, 24.4 (CH_2-3); MS (ESI): *m/z* = 318 $[M+Na]^+$ 100%.

(2*S,5*S**)-1-*tert*-Butyl-2-methyl-5-(methylsulfonyloxy)piperidine-1,2-dicarboxylate *cis*-13b.**

Mesylation of alcohol *cis*-**8b** (456 mg, 1.76 mmol) afforded after purification by flash column chromatography (cyclohexane/EtOAc 6:4) mesylate *cis*-**13b** as a colourless oil (462 mg, 78%). R_f = 0.25 (cyclohexane/EtOAc 6:4); ν_{max}(neat)/cm^{-1} 2976, 2873, 1739, 1695, 1354, 1333, 1170, 1147, 953; δ_H (250 MHz, $CDCl_3$; Me_4Si) 4.90–4.45 (2 H, m, 2-H, 5-H), 4.43–4.15 (1 H, m, 6-H), 3.72 (3 H, s, CO_2CH_3), 3.10–2.75 (4 H, m including s for CH_3SO_2, 6-H), 2.40–2.05 (2 H, m, 3-H, 4-H), 1.90–1.30 (11 H, m, 3-H, 4-H, *t*-Bu); δ_C (63 MHz, $CDCl_3$) 171.2 ($\underline{C}O_2CH_3$), 155.0, 154.7 ($\underline{C}O_2$-*t*-Bu), 81.1 ($\underline{C}Me_3$), 75.3, 75.0 (CH-5), 53.7, 52.4 (CH-2), 52.4 ($CO_2\underline{Me}$), 45.8, 44.5 (CH_2-6), 38.7 (CH_3SO_2), 28.2 (CH_2-4 and $C\underline{Me}_3$), 24.7 (CH_2-3); MS (ESI): *m/z* = 360 $[M+Na]^+$ 100%.

(2*S,5*R**)-1-*tert*-Butyl-2-methyl-5-(methylsulfonyloxy)piperidine-1,2-dicarboxylate *trans*-13b.**

Mesylation of alcohol *trans*-**8b** (2 g, 7.72 mmol) afforded after purification by flash column chromatography (cyclohexane/EtOAc 1:1) mesylate *trans*-**13b** as a colourless oil (1.9 g, 73%). R_f = 0.29 (EtOAc/cyclohexane 1:1); ν_{max}(neat)/cm^{-1} 2971, 1736, 1692, 1336, 1165, 1147, 902; δ_H (250 MHz, $CDCl_3$; Me_4Si) 5.10–4.70 (2 H, m, 2-H, 5-H), 4.45–4.15 (1 H, m, 6-H), 3.72 (3 H, s, CO_2CH_3), 3.40–2.90 (4 H, m, CH_3SO_2, 6-H), 2.25–1.90 (3 H, m, 3-H, 4-H), 1.75–1.30 (10 H, m, 4-H, *t*-Bu); δ_C (63 MHz, $CDCl_3$) 170.9, 170.6 ($\underline{C}O_2CH_3$), 155.0 ($\underline{C}O_2$-*t*-Bu), 80.4 ($\underline{C}Me_3$), 74.2, 74.1 (CH-5), 53.8, 52.4 (CH-2), 52.0 ($CO_2\underline{C}H_3$), 45.4, 44.0 (CH_2-6), 38.3 (CH_3SO_2), 27.9 ($C\underline{Me}_3$), 25.6 (CH_2-4), 20.2 (CH_2-3); MS (ESI): *m/z* = 360 $[M+Na]^+$ 100%.

(2*S,5*R**)-Dimethyl 5-(tosyloxy)piperidine-1,2-dicarboxylate** *trans*-**14a.**

Tosylation of alcohol *trans*-**8a** (400 mg, 1.84 mmol) afforded after purification by flash column chromatography (cyclohexane/EtOAc 6:4), tosyloxy compound *trans*-**14a** as a white powder (431 mg, 63%). R_f = 0.44 (EtOAc/cyclohexane 1:1); m.p. = 116–118 °C (from Et_2O); (Found: C, 51.67; H, 5.68; N, 3.77. $C_{16}H_{21}NO_7S$ requires C, 51.74; H, 5.70; N, 3.77); δ_H (250 MHz, $CDCl_3$; Me_4Si) 7.77 (2 H, d, *J* 8.0, $H_{Ar.}$), 7.32 (2 H, d, *J* 8.0, $H_{Ar.}$), 5.05–4.76 (1 H, m, 2-H), 4.74–4.60 (1 H, m, 5-H), 4.15–4.00 (1 H, m, 6-H), 3.75–3.55 (6 H, m, $2\times CO_2CH_3$), 3.30–3.00 (1 H, m, 6-H), 2.44 (3 H, s, CH_3SO_2), 2.25–1.35 (4 H, m, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 171.7 ($\underline{C}O_2CH_3$), 156.9 ($N\underline{C}O_2CH_3$), 145.0 ($C_{Ar.}$), 134.0 ($C_{Ar.}$), 130.0 ($CH_{Ar.}$), 127.8 ($CH_{Ar.}$), 74.3 (CH-5), 53.7, 53.3, 52.5 (CH-2, $NCO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 45.3, 44.9 (CH_2-6), 25.6 (CH_2-4), 21.7 (Ar-$\underline{C}H_3$), 20.5 (CH_2-3); MS (ESI): *m/z* = 394 $[M+Na]^+$ 100%.

(2*S,5*S**)-Dimethyl 5-(tosyloxy)piperidine-1,2-dicarboxylate** *cis*-**14a.**

Tosylation of alcohol *cis*-**8a** (93 mg, 0.43 mmol) afforded, after purification by flash column chromatography (cyclohexane/EtOAc 6:4) pure *cis*-tosyloxy compound *cis*-**14a** as a colourless oil (108 mg, 67%). R_f = 0.24 (cyclohexane/AcOEt 6:4); δ_H (250 MHz, $CDCl_3$; Me_4Si) 7.78 (2 H, d, *J* 8.1, $H_{Ar.}$), 7.33 (2 H, d, *J* 8.1, $H_{Ar.}$), 4.90–4.78 (0.6 H, m, 2-H), 4.74–4.62 (0.4 H, m, 2-H), 4.45–4.26 (1 H, m, 5-H), 4.24–4.05 (1 H, m, 6-H), 3.80–3.60 (6 H, m, $2\times CO_2CH_3$), 3.05–2.75 (1 H, m, 6-H), 2.43 (3 H, s, CH_3SO_2), 2.35–2.20 (1 H, m, 3-H), 2.15–

1.81 (1 H, m, 4-H), 1.79–1.30 (2 H, m, 3-H, 4-H); δ_C (63 MHz, $CDCl_3$) 170.9 ($\underline{C}O_2CH_3$), 156.3, 155.9 ($N\underline{C}O_2CH_3$), 145.1 ($C_{Ar.}$), 133.9 ($C_{Ar.}$), 130.0 ($CH_{Ar.}$), 127.7 ($CH_{Ar.}$), 75.2 (CH-5), 53.3, 52.9, 52.5 (CH-2, $NCO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 45.2, 44.7 (CH_2-6), 27.7 (CH_2-4), 25.0, 24.7 (CH_2-3), 21.7 (CH_3-Ar); MS (ESI): m/z = 394 $[M+Na]^+$ 100%.

(2*S,5*R**)-Dimethyl *trans*-5-aminopiperidine-1,2-dicarboxylate** *trans*-**15a.**

To a solution of the azido methyl ester *trans*-**5a** (0.7 g, 2.89 mmol) in saturated HCl/MeOH (75 mL) was added 10% Pd/C (270 mg) and the heterogeneous mixture was stirred under atmospheric pressure of dihydrogen at r.t. for 4 h. The mixture was filtered through a pad of Celite®, washed with MeOH, and the filtrate was concentrated in vacuo; to the resulting powder was added methanol (3×30 mL) and re-evaporated then washed with anhydrous Et_2O (3×30 mL), and finally dried under vacuum (0.01 mbar) to afford the chlorohydrate of amino compound *trans*-**15a** as a white solid (710 mg, 97%). δ_H (250 MHz, CD_3OD; Me_4Si) 4.95–4.85 (1 H, m, 2-H), 4.30–4.02 (1 H, m, 6-H), 3.85–3.65 (6 H, m, 2×CO_2CH_3), 3.60–3.51 (1 H, m, 5-H), 3.40–3.25 (1 H, m, 6-H), 2.30–1.70 (4 H, m, 3-H, 4-H); δ_C (63 MHz, CD_3OD) 172.6 ($\underline{C}O_2CH_3$), 158.6 ($N\underline{C}O_2CH_3$), 55.0, 54.8 (CH-2), 54.1, 54.3 (2×$CO_2\underline{C}H_3$), 46.5 (CH-5), 44.3, 44.0 (CH_2-6), 23.9 (CH_2-4), 20.9 (CH_2-3); MS (ESI): m/z = 217 $[M+H]^+$ 100%.

(2*S,5*S**)-Dimethyl *cis*-5-aminopiperidine-1,2-dicarboxylate** *cis*-**15a.**

Hydrogenolysis of azido compound *cis*-**5a** (2.08 g, 8.60 mmol) following the same procedure as above afforded the chlorohydrate of amino compound *cis*-**15a** as a white solid (2.02 g, 93%). δ_H (250 MHz, CD_3OD; Me_4Si) 4.95–4.80 (1 H, m, 2-H), 4.40–4.20 (1 H, m, 6-H), 3.80–3.60 (6 H, m, 2×CO_2CH_3), 3.35–3.13 (1 H, m, 5-H), 3.12–2.85 (1 H, m, 6-H), 2.45–2.25 (1 H, m, 3-H), 2.15–2.01 (1 H, m, 4-H), 1.99–1.75 (1 H, m, 3-H), 1.55–1.25 (1 H, m, 4-H); δ_C (63 MHz, CD_3OD) 172.3 ($\underline{C}O_2CH_3$), 157.9, 157.8 ($N\underline{C}O_2CH_3$), 54.7, 54.4 (CH-2), 53.9, 53.1 (2×$CO_2\underline{C}H_3$), 47.9 (CH-5), 44.7, 44.5 (CH_2-6), 26.4 (CH_2-4), 25.9, 25.7 (CH_2-3); MS (ESI): m/z = 217 $[M+H]^+$ 100%.

(2*S,5*S**)-*tert*-Butyl 2-methyl *cis*-5-aminopiperidine-1,2-dicarboxylate** *cis*-**15b.**

To a solution of the azido methyl ester *cis*-**5b** (366 mg, 1.29 mmol) in neutral MeOH (30 mL) was added 10% Pd/C (133 mg) then stirred under atmospheric pressure of dihydrogen at r.t. for 2 h. The mixture was filtered through a pad of Celite®, washed with MeOH, and the filtrate was concentrated in vacuo to afford the amino compound as a colourless oil (260 mg, 78%) which was involved directly in the guanylating step, *otherwise it involves intramolecular lactamization when left neat at room temperature*. δ_H (250 MHz, CD_3OD; Me_4Si) 4.94–4.59 (1 H, m, 2-H), 4.19–3.93 (1 H, m, 6-H), 3.70 (3 H, s, CO_2CH_3), 2.85–2.33

(2 H, m, 5-H, 6-H), 2.33–2.17 (1 H, m, 3-H), 1.94–1.57 (4 H, m, 3-H, 4-H, *N*H), 1.45, 1.42 (9 H, s, CMe_3), 1.15–0.94 (1 H, m, 4-H).

(2*S,5*R**)-*tert*-Butyl 2-methyl trans-5-aminopiperidine-1,2-dicarboxylate *trans*-15b.**

Similarly to its *cis* isomer, hydrogenolysis of *trans*-**5b** (104 mg, 0.37 mmol) led to compound *trans*-**15b** as a colourless oil (90 mg, 95%). ν_{max}(neat)/cm^{-1} 3374, 2971, 2950, 2930, 2873, 1739, 1692, 1633, 1452, 1411, 1390, 1364, 1338, 1248, 1204, 1152, 1121, 1018; δ_H (250 MHz, CD_3OD; Me_4Si) 4.85–4.53 (1 H, m, 2-H), 3.82–3.66 (1 H, m, 6-H), 3.61 (3 H, s, CO_2CH_3), 3.18–2.92 (2 H, m, 5-H, 6-H), 2.25 (2 H, br s, *N*H), 2.08–1.82 (2 H, m), 1.55–1.42 (2 H, m), 1.34 (9 H, s, CMe_3); δ_C (63 MHz, CD_3OD) 172.1 ($\underline{C}O_2CH_3$), 156.4, ($\underline{C}O_2$-*t*-Bu), 80.4 ($\underline{C}Me_3$), 54.1, 53.5 (CH-2), 52.1 ($CO_2\underline{C}H_3$), 48.2, 47.4 (CH_2-6), 44.5 (CH-5), 28.3 ($\underline{C}Me_3$), 27.6 (CH_2-4), 20.4 (CH_2-3).

(2*S,5*S**)-5-Amino-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid *cis*-15'b.**

To a solution of the azido acide *cis*-**5'b** (115 mg, 0.43 mmol) in MeOH (10 mL) was added 10% Pd/C (42 mg) then the mixture was stirred under atmospheric pressure of dihydrogen, at r.t. for 16 h. The mixture was filtered through a pad of Celite®, washed with MeOH, and the filtrate was concentrated in vacuo. Purification by C-18 reverse phase column chromatography (H_2O/MeOH 95:5) afforded the amino compound *cis*-**15'b** as a white solid (65 mg, 63%). ν_{max}(neat)/cm^{-1} 2971, 2868, 1687, 1625, 1555, 1460, 1444, 1416, 1387, 1364, 1341, 1300, 1289, 1245, 1168, 1160, 1111, 1070, 1052, 1023; δ_H (250 MHz, D_2O) 4.70–4.53 (1 H, m, 2-H), 4.40–4.00 (1 H, m, 6-H), 3.55–3.05 (2 H, m, 5-H, 6-H), 2.45–2.01 (2 H, m, 3-H, 4-H), 1.99–1.70 (1 H, m, 3-H), 1.68–1.31 (10 H, m, CMe_3, 4-H); δ_C (63 MHz, CD_3CN) 177.7 (CO_2H), 157.5 ($\underline{C}O_2$-*t*-Bu) 81.6 ($\underline{C}Me_3$), 56.9 (CH-2), 47.4 (CH-5), 42.8 (CH_2-6), 28.1, 25.1 ($C\underline{Me}_3$, CH_2-3, CH_2-4); MS (ESI): *m/z* = 245 $[M+ H]^+$ 100%.

(2*S,5*R**)-5-Amino-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid *trans*-15'b.**

As for *cis* isomer, hydrogenolysis of *trans*-**5'b** (130 mg, 0.48 mmol) afforded, after purification by C-18 reverse phase column chromatography (H_2O), the amino compound *trans*-**15'b** as a white solid (84 mg, 72%). m.p. = 225–230 °C). δ_H (250 MHz, D_2O) 4.70–4.42 (1 H, m, 2-H), 4.10–3.90 (1 H, m, 6-H), 3.69–3.40 (2 H, m, 5-H, 6-H), 2.35–2.10 (1 H, m, 3-H), 2.00–1.65 (3 H, m, 3-H, 4-H), 1.47 (9 H, s, CMe_3); δ_C (63 MHz, CD_3CN) 177.6 (CO_2H), 158.2 ($N\underline{C}O_2t$Bu), 81.6 ($\underline{C}Me_3$), 57.9, 56.6 (CH-2), 47.1 (CH-5), 45.1, 44.2 (CH_2-6), 28.8 ($C\underline{Me}_3$), 24.9 (CH_2-4), 22.0 (CH_2-3); MS (ESI): *m/z* = 245 $[M+ H]^+$ 100%.

(2*S,5*S**)-5-*N,N'*-bis(Benzyloxycarbonyl)guanidino)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid *cis*-16'b.**

To the amino acid *cis*-**15’b** (50 mg, 0.20 mmol) in DCM (4 mL), were added *N*,*N*’-bis(benzyloxycarbonyl)-*N*’’-trifluoromethane-sulfonylguanidine (184 mg, 0.40 mmol) and triethylamine (56 µL, 0.40 mmol). The heterogeneous mixture was stirred at r.t. for 4 days, acidified with 10% aqueous citric acid (3 mL) and then extracted with DCM (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (DCM→DCM/MeOH 95:5) afforded the 5-guanidino compound *cis*-**16’b** as a colourless oil (25 mg, 22%). R_f = 0.38 (DCM/MeOH 9:1); ^{1}H NMR: δ_H (250 MHz, $CDCl_3$; Me_4Si) 8.18 (1 H, br s, *N*H), 7.50–7.20 (10 H, m, $H_{Ar.}$), 5.25–5.00 (4 H, m, 2×OC$\underline{H}_2$Ph), 4.96–4.66 (1 H, m, 2-H), 4.35–3.97 (2 H, m, 5-H, 6-H), 2.83–2.55 (1 H, m, 6-H), 2.35–2.16 (1 H, m, 3-H), 2.08–1.92 (1 H, m, 4-H), 1.90–1.68 (1 H, m, 3-H), 1.41 (9 H, s, CMe_3), 1.35–1.16 (1 H, m, 4-H); δ_C (63 MHz, $CDCl_3$) 176.4 (CO_2H), 164.0, 155.8, 154.0 (N-C=O, C=N), 136.9, 134.7 ($C_{Ar.}$), 129.1, 128.9, 128.7, 128.6, 128.3, 128.2 ($CH_{Ar.}$), 81.3 ($\underline{C}Me_3$), 68.5, 67.5 (2×O$\underline{C}H_2$Ph), 53.6, 52.5 (CH-2), 46.8 (CH-5), 45.9 (CH_2-6), 28.5 (C$\underline{Me_3}$), 27.7 (CH_2-4), 25.2 (CH_2-3); MS (ESI): *m/z* = 555 $[M+H]^+$ 100%.

(2*S,5*R**)-5-*N*,*N'*-bis(Benzyloxycarbonyl)guanidino)-1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid** *trans*-**16’b.**

To the amino acid *trans*-**15’b** (53 mg, 0.22 mmol) in DCM (3 mL), were added *N*,*N*’-bis(benzyloxycarbonyl)-*S*-methyl-isothiourea (220 mg, 0.61 mmol) and triethylamine (120 µL, 0.86 mmol). The heterogeneous mixture was stirred at r.t. for 6 days then worked up as for compound *cis*. Purification by flash column chromatography (DCM→DCM/MeOH 95:5) afforded the 5-guanidino compound *trans*-**16’b** as a white solid (60 mg, 58%). R_f = 0.36 (DCM/MeOH 9:1); ν_{max}(neat)/cm^{-1} 3322, 3281, 2971, 1726, 1695, 1633, 1617, 1568, 1452, 1423, 1380, 1364, 1346, 1333, 1300, 1240, 1199, 1170, 1139, 1121, 1049; δ_H (250 MHz, $CDCl_3$; Me_4Si) 11.57 (1 H, br s, *N*HZ), 8.65 (1 H, br s, *N*H), 7.33–7.10 (10 H, m, $H_{Ar.}$), 5.12–4.67 (5 H, m, 2×OC$\underline{H}_2$Ph, 2-H), 4.38–3.92 (2 H, m, 5-H, 6-H), 3.15–2.90 (1 H, m, 6-H), 2.15–1.96 (1 H, m, 3-H), 1.94–1.68 (1 H, m, 3-H, 4-H), 1.65–1.40 (1 H, m, 4-H), 1.30 (9 H, s, CMe_3); δ_C (63 MHz, $CDCl_3$) 176.3 (CO_2H), 163.8, 156.0, 155.6, 154.0 (N-C=O, C=N), 136.9, 134.7 ($C_{Ar.}$), 129.0, 128.8, 128.7, 128.6, 128.2, 128.1 ($CH_{Ar.}$), 81.3 ($\underline{C}Me_3$), 68.4, 67.4 (2×O$\underline{C}H_2$Ph), 54.3, 53.1 (CH-2), 45.6 (CH_2-6), 44.8 (CH-5), 28.3 (C$\underline{Me_3}$), 25.0 (CH_2-4), 21.3 (CH_2-3); MS (ESI): *m/z* = 555 $[M+H]^+$ 100%.