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

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Preparation of substrates 3

\textit{rac-Dimethyl 3,4-dihydropyridine-1,2(2\text{H})-dicarboxylate rac-3a.}

Into an undivided beaker type cell with cooling mantle equipped with graphite electrodes plates (15 cm\textsuperscript{2}), was introduced 1\textsubscript{a} (10 g, 49.8 mmol), tetrabutyl ammonium 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\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. To the crude product (neat), was added NH\textsubscript{4}Cl (15.8 g, 0.29 mol) and the mixture was heated for 5 h at 80 °C under reduced pressure (10 mm Hg). Et\textsubscript{2}O (100 mL) was added; after filtration through a pad of Celite\textsuperscript{®} the white precipitate was washed with Et\textsubscript{2}O (100 mL) and the filtrate was concentrated in vacuo. Purification by column chromatography (cyclohexane/EtOAc 8:2, and up to 1:1) afforded enecarbamate 3\textsubscript{a} (8.58 g, 73% yield) as a colourless oil: \(R_t = 0.49\) (EtOAc/cyclohexane 1:1); \(\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}\) 2955, 2846, 1747, 1706, 1656, 1441, 1349, 1203; \(\delta_{\text{H}}\) (250 MHz, CDCl\textsubscript{3}; Me\textsubscript{4}Si) 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\textsubscript{2}CH\textsubscript{3}), 3.71 (4.2 H, s, CO\textsubscript{2}Me and NCO\textsubscript{2}CH\textsubscript{3}), 2.38–2.29 (1 H, m, 4-H), 2.02–1.86 (3 H, m, 3-H, 4-H); \(\delta_{\text{C}}\) (63 MHz, CDCl\textsubscript{3}) 170.9, 169.9 (CO\textsubscript{2}CH\textsubscript{3}), 153.5 (NCO\textsubscript{2}CH\textsubscript{3}), 124.2, 123.8 (CH-6), 105.0, 104.8 (CH-5), 53.6, 53.3, 52.8, 52.0 (CH-2, CO\textsubscript{2}CH\textsubscript{3}, NCO\textsubscript{2}CH\textsubscript{3}), 23.2, 23.1 (CH\textsubscript{2}-4), 18.1, 17.9 (CH\textsubscript{2}-3).

\textit{rac-1-tert-Butyl 2-methyl 3,4-dihydropyridine-1,2(2\text{H})-dicarboxylate rac-3b.}

After electrolysis of 1\textsubscript{b} (9.86 g, 40.57 mmol) in presence of tetrabutylammonium tetrafluoroborate (1.79 g, 5.43 mmol) and CH\textsubscript{3}OH (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\textsuperscript{®} and washing with Et\textsubscript{2}O, the filtrate was concentrated in vacuo and the residue purified by column chromatography (cyclohexane/EtOAc 85:15). Enecarbamate 3\textsubscript{b} was isolated as a colourless oil (9.05 g, 93%
yield): $R_f = 0.52$ (EtOAc/cyclohexane 1:1); $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2977, 1752, 1707, 1655, 1352, 1166, 1069, 770; $\delta_{\text{t}}$(250 MHz, CDCl$_3$; Me$_4$Si) 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$_2$CH$_3$), 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, $\times$s, t-Bu); $\delta_C$ (63 MHz, CDCl$_3$) 171.8, 171.4 (C O$_2$CH$_3$), 152.3, 152.2 (C O$_2$t-Bu), 124.8, 124.3 (CH-6), 104.5, 104.0 (CH-5), 81.2, 81.0 (CMe$_3$), 54.3, 53.0 (CH-2), 52.2 (CO$_2$CH$_3$), 28.1, 28.0 (CMe$_3$), 23.5, 23.4 (CH$_2$-4), 18.4, 18.2 (CH$_2$-3).

(5R*,6S*,8aS*)-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); $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2946, 2095, 1741, 1402, 1360, 1236, 1196, 1167, 1088, 1030, 995; $\delta_{\text{H}}$(250 MHz, CDCl$_3$; Me$_4$Si) 4.82 (1 H, br s, 5-H), 4.47 (1 H, t, $J$ 8.0 and $J$ 8.0, CH$_2$O), 3.99-3.75 (3 H, m, 8a-H, 6-H, CH$_2$O), 3.32 (3 H, s, OCH$_3$), 2.10-1.55 (4 H, m, 7-H, 8-H); $\delta_C$ (63 MHz, CDCl$_3$) 157.3 (NCO$_2$), 82.0 (CH-5), 68.9 (CH$_2$O), 57.3 (CH-6), 55.7 (OCH$_3$), 49.3 (CH-8a), 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$_3$SiH (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%).

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

$R_f = 0.28$ (EtOAc/Cyclohexane 90:10); $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2928, 2089, 1743, 1424, 1332, 1265, 1152, 1097, 1060, 959; $\delta_{\text{t}}$(250 MHz, CDCl$_3$; Me$_4$Si) 4.41 (1H, dd, $J$ 8.5 and $J$ 8.5, CH$_2$O), 4.01-3.79 (3 H, m, 5-H, 6-H, CH$_2$O), 3.76-3.61 (1 H, m, 8a-H), 3.68–3.55 (1 H, m, 8a-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); $\delta_C$ (63 MHz, CDCl$_3$) 157.3 (NCO$_2$), 68.0 (CH$_2$O), 54.7 (CH-6), 53.5 (CH-8a), 44.2 (CH$_2$-5), 26.4 (CH$_2$-7), 24.8 (CH$_2$-8); MS (ESI): $m/z = 183$ [M+H]$^+$ 100%.

(6R*,8aS*)-6-Azido-3-oxohexahydro-1H-oxazolo[3,4-a]pyridine trans-5c.
$R_f = 0.41$ (EtOAc/Cyclohexane 90:10); $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2923, 2099, 1745, 1424, 1317, 1251, 1164, 1125, 1063, 966; $\delta_\text{H}$ (250 MHz, CDCl$_3$; Me$_4$Si) 4.38 (1H, dd, $J$ 8.0 and $J$ 8.0, CH$_2$O), 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$_2$O), 3.70-3.50 (1 H, m, 6-H), 3.46-3.25 (1H, m, 2-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); $\delta_\text{C}$ (63 MHz, CDCl$_3$) 156.7 (NCO$_2$), 67.8 (CH$_2$O), 55.7 (CH-6), 53.4 (CH-8$\alpha$), 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$_2$O (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%).

$\nu_{\text{max}}$(neat)/cm$^{-1}$ 2976, 2098, 1736, 1695, 1473, 1408, 1392, 1367, 1325, 1245, 1147, 1052, 1005; $\delta_\text{H}$ (250 MHz, CDCl$_3$; Me$_4$Si) 10.44 (1 H, s, CO$_2$H), 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); $\delta_\text{C}$ (63 MHz, CDCl$_3$) 175.3, 175.2 (CO$_2$H), 155.3, 155.0 (NCO$_2$-t-Bu), 81.2 (CMe$_3$), 56.1 (CH-5), 53.4, 52.3 (CH-2), 45.6, 44.5 (CH$_2$-6), 28.0 (CMe$_3$), 26.6 (CH$_2$-4), 24.9, 24.7 (CH$_2$-3); MS (ESI): $m/z = 171$ [M-C$_5$H$_8$O$_2$+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%). $\nu_{\text{max}}$(neat)/cm$^{-1}$ 2971, 2113, 1741, 1620, 1475, 1436, 1392, 1372, 1314, 1263, 1248, 1204, 1168, 1147, 1132, 1031, 1013; $\delta_\text{H}$ (250 MHz, CDCl$_3$; Me$_4$Si) 5.15-4.70 (1 H, m, 2-H), 4.27–4.00 (1 H, m, 6-H), 4.15–3.00 (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); $\delta_\text{C}$ (63 MHz, CDCl$_3$) 177.3 (CO$_2$H), 155.9 (CO$_2$-t-Bu), 81.4 (CMe$_3$), 55.1 (CH-5), 54.3, 53.0 (CH-2), 44.4, 43.8 (CH$_2$-6), 28.4 (CMe$_3$), 25.1 (CH$_2$-4), 21.0 (CH$_2$-3); MS (ESI): $m/z = 171$ [M-C$_5$H$_8$O$_2$+H]$^+$ 100%.

**Halogenomethoxylation of 3**

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

(2S*,5R*,6S*)-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-trans; 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); $\nu_{\text{max}}($neat)/cm$^{-1}$ 2954, 1739, 1706, 1440; $\delta_H$ (250 MHz, CDCl$_3$; Me$_4$Si) 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$_2$CH$_3$), 3.70 (3 H, s, NCO$_2$CH$_3$), 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); $\delta_C$ (63 MHz, C$_6$D$_6$) 171.4 (CO$_2$CH$_3$), 157.0, 156.4 (NCO$_2$CH$_3$), 86.0, 85.5 (CH-6), 56.8, 56.1 (6-OCH$_3$), 52.9 (CO$_2$CH$_3$), 51.5, 51.4 (CH-2), 50.9, 50.4 (NCO$_2$CH$_3$), 49.8, 49.4 (CH-5), 23.9, 23.8 (CH$_2$-4), 19.7, 19.5 (CH$_2$-3).

(2S*,5R*,6S*)-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); $\delta_H$ (250 MHz, CDCl$_3$; Me$_4$Si) 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$_2$CH$_3$), 3.69 (3 H, br s, NCO$_2$CH$_3$), 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); $\delta_C$ (63 MHz, CDCl$_3$) 171.8 (CO$_2$CH$_3$), 157.1, 156.6 (NCO$_2$CH$_3$), 87.1, 86.4 (CH-6), 56.9, 56.5 (OCH$_3$), 53.5, 52.8, 52.1 (CO$_2$CH$_3$), 50.8, 50.2 (CH-2), 29.4, 29.0 (CH-5), 24.8 (CH$_2$-4), 21.3, 21.0 (CH$_2$-3).

(5R*,6S*,8aS*)-6-Iodo-5-methoxy-tetrahydro-1H-oxazolo[3,4-a]pyridin-3(5H)-one 6’c.
Prepared according to the above procedure, starting from enecarbamate 3e (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. $R_t = 0.27$ (cyclohexane/EtOAc 5:5); $\delta_H$ (250 MHz, CDCl$_3$;
Me₄Si) 5.16 (1 H, br s, 5-H), 4.52 (1 H, dd, J 7.7 and J 7.7, CH₂O), 4.43 (1 H, br s, 6-H), 4.07–3.84 (2 H, m, 8a-H, CH₂O), 3.33 (3 H, s, OCH₃), 2.25–1.65 (4 H, m, 8-H, 7-H); δₐ (63 MHz, CDCl₃) 157.4 (NCO₂), 85.6 (CH-5), 69.1 (CH₂O), 55.8 (OCH₃), 49.5 (CH-8a), 27.2 (CH₂), 26.8 (CH-6), 26.6 (CH₂).

(2S*,5R*)-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 Et₃SiH (230 µL, 1.45 mmol) in DCM (19 mL), was added BF₃.OEt₂ (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 NaHCO₃ (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%). νmax(neat)/cm⁻¹ 2954, 2849, 1738, 1699, 1445, 1365, 1247, 1206, 1151, 1115, 1015, 954, 810, 785, 768; δ₁H (250 MHz, CDCl₃; Me₄Si) 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, CO₂CH₃, NCO₂CH₃), 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); δₐ (63 MHz, CDCl₃) 170.9 (CO₂CH₃), 156.2, 155.8 (NCO₂CH₃), 53.2, 52.9 (CH-2), 52.5, 51.8 (CO₂CH₃), 48.1 (C-6), 47.9 (C-5), 28.7 (C-4), 20.7 (C-3).

(2S*,5S*)-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), we re 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%); νmax(neat)/cm⁻¹ 2955, 1740, 1702, 1443, 1404, 1310, 1206, 1150, 1121, 1004, 769, 727; δ₁H (250 MHz, CDCl₃; Me₄Si) 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, CO₂CH₃, NCO₂CH₃), 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); δₐ (63 MHz, CDCl₃) 170.9 (CO₂CH₃), 155.8, 155.5 (NCO₂CH₃), 53.3 (CH-2), 53.1 (CO₂CH₃), 52.9 (CH-2), 52.5 (CO₂CH₃), 49.0, 48.7 (CH₂-6), 44.5 (CH-5), 32.5 (CH₂-4), 28.0, 27.8 (CH₂-3).

(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 \text{ (EtOAc/MeOH 95:5); } \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 3352, 2931, 1742, 1435, 1253, 1071; \delta_{\text{H}} (250 \text{ MHz, CDCl}_3; \text{Me}_4\text{Si}) 4.39 \text{ (1 H, t, } J 8.5 \text{ t, CH}_2\text{O)}, 4.00 \text{ (1 H, ddd, } J 12.8, 5.4 \text{ and } 1.8, 6-\text{H}), 3.88 \text{ (1 H, t, } J 8.5, \text{ CH}_2\text{O}), 3.72–3.54 \text{ (2 H, m, 2-\text{H}, 5-\text{H})}, 2.63 \text{ (1 H, dd, } J 12.8, \text{ and } 10.3, 6-\text{H}), 2.56 \text{ (1 H, br s, OH)}, 2.18–2.06 \text{ (1 H, m), 1.94–1.83 (1 H, m), 1.47–1.37 (1 H, m)}; \delta_{\text{C}} (63 \text{ MHz, CDCl}_3) 157.0 \text{ (NC}_2\text{O}), 67.7 \text{ (CH}_2\text{O}), 65.7 \text{ (CH-6), 53.5 (CH-8a), 47.7 (CH}_2\text{-5), 31.9 (CH}_2\text{-7), 29.1 (CH}_2\text{-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 \text{ (EtOAc); } \nu_{\text{max}}(\text{neat})/\text{cm}^{-1} 2925, 2854, 1717, 1648, 1430, 1247; \delta_{\text{H}} (250 \text{ MHz, CDCl}_3; \text{Me}_4\text{Si}) 4.59-4.50 \text{ (1 H, m, CH}_2\text{O)}, 4.31 \text{ (1 H, d, } J 18.1, 5-\text{H}), 4.12–3.98 \text{ (2 H, m, 8a-\text{H}, CH}_2\text{O}), 3.65 \text{ (1 H, d, } J 18.1, 5-\text{H}), 2.68 \text{ (1 H, dt, } J 16.8 \text{ and } 4.0, 7-\text{H}), 2.53–2.38 \text{ (1 H, m, 7-\text{H}), 2.23–2.12 (1 H, m, 8-H), 2.03–1.84 (1 H, m, 8-H)}; \delta_{\text{C}} (63 \text{ MHz, CDCl}_3) 202.4 \text{ (C-5), 156.2 (NC}_2\text{O), 67.2 (CH}_2\text{O), 51.4 (CH-8a), 50.9 (CH-5), 36.8 (CH}_2\text{-7), 27.7 (CH}_2\text{-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. 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 MgSO₄, and concentrated in vacuo. Products were purified by flash column chromatography (unless otherwise indicated).

Method B (With Oxone® in H₂O): to a ca. 0.5 M solution of enecarbamate 3 in acetone/water (v/v: 4/1), were added solid NaHCO₃ (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 NaHCO₃ (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.

(2S*,5R*)-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.

Rᵣ = 0.30 (EtOAc/Cyclohexane 1:1); νₘₐ₅(neat)/cm⁻¹ 2956, 1734, 1699, 1444, 1369, 1226, 1120, 1021, 770; δ₁ (250 MHz, CDCl₃; Me₄Si) 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, CO₂CH₃), 3.70 (3 H, s, CO₂CH₃), 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); δC (63 MHz, CDCl₃) 171.5, 170.2 (CO₂CH₃, OAc), 157.0, 156.4 (NCO₂CH₃), 66.1 (CH-2), 53.8, 53.5 (CH-5), 52.8, 52.1
(CO$_2$CH$_3$), 44.5 (CH$_2$-6), 24.5 (CH$_2$-4), 20.9 (OCO$_2$CH$_3$), 20.8 (CH$_2$-3); MS (ESI): m/z = 260 [M+H]$^+$ 100%.

**($2S^*,5R^*$)-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); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2972, 2953, 1738, 1696, 1448, 1416, 1364, 1337, 1231, 1199, 1172, 1149, 1120, 1021; $\delta_t$ (250 MHz, CDCl$_3$; Me$_4$Si) 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$_2$CH$_3$), 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); $\delta_c$ (63 MHz, CDCl$_3$) 171.8, 170.0 (CO$_2$CH$_3$, OAc), 155.4 (NCO$_2$-t-Bu), 80.1 (CMe$_3$), 66.4, 66.2 (CH-5), 54.3, 52.8 (CH-2), 52.0 (CO$_2$CH$_3$), 44.6, 43.9 (CH$_2$-6), 28.1 (CMe$_3$), 24.6, 24.4 (CH$_2$-4), 20.9 (H$_3$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.

**($6R^*,8aS^*$)-6-acetoxy-3-oxohexahydro-1H-oxazolo[3,4-a]pyridine trans-11c:** $R_f = 0.34$ (EtOAc/Cyclohexane 8:2); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2962, 2871, 1732, 1438, 1251, 1237, 1054, 751; $\delta_t$ (250 MHz, CDCl$_3$; Me$_4$Si) 4.76–4.60 (1 H, m, 6-H), 4.41 (1H, dd, $J$ 8.6 and $J$ 8.6, CH$_2$O), 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$_2$O), 3.68–3.55 (1 H, m, 8a-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); $\delta_c$ (63 MHz, CDCl$_3$) 169.8 (OAc), 156.5 (NCO$_2$), 67.7 (CH$_2$O), 67.3 (CH-6), 53.4 (CH-8a), 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%.

**($6S^*,8aS^*$)-6-acetoxy-3-oxohexahydro-1H-oxazolo[3,4-a]pyridine cis-11c:** $R_f = 0.22$ (EtOAc/Cyclohexane 8:2); $\nu_{\text{max}}$ (neat)/cm$^{-1}$ 2927, 1722, 1435, 1254, 1228, 1043, 1019, 758;
δ_H (250 MHz, CDCl₃; Me₄Si) 4.98–4.94 (1 H, m, 6-H), 4.41 (1 H, dd, J 8.3 and 8.3, CH₂O), 4.04–3.92 (2 H, m, CH₂O, 5-H), 3.78–3.66 (1 H, m, 8α-H), 3.03 (1 H, dd, J 14.6 and 2.1, 5-H), 2.15–1.99 (4 H, including s for OAc), 1.89–1.60 (3 H, m); δ_C (63 MHz, CDCl₃) 170.3 (OAc), 157.5 (NCO₂), 67.8 (CH₂O), 65.6 (CH-6), 53.6 (CH-8α), 44.5 (CH-5), 26.5 (CH-7), 24.4 (CH₂-8), 20.9 (CH₃); MS (ESI): m/z = 217 [M+NH₄]⁺ 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 NH₄Cl and the organic layer was extracted with DCM. The combined organic layers were washed with H₂O, dried over MgSO₄ and concentrated in vacuo then submitted to purification by column chromatography.

Mesylation: to a solution of alcohol 8 in DCM, were added Et₃N (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.

(2S*,5S*)-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, CDCl₃; Me₄Si) 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, CO₂CH₃), 3.10–2.85 (4 H, m, 6-H, CH₃SO₂), 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, CDCl₃) 170.8 (CO₂CH₃), 156.0, 155.8 (NCO₂CH₃), 74.5 (CH-5), 53.5, 53.1, 52.3 (CH-2, NCO₂CH₃, CO₂CH₃), 45.2, 44.8 (CH₂-6), 38.4 (CH₃SO₂), 27.8 (CH₂-4), 24.8, 24.4 (CH₂-3); MS (ESI): m/z = 318 [M+Na]⁺ 100%.

(2S*,5S*)-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, CDCl₃; Me₄Si) 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, CO₂CH₃), 3.10–2.75 (4 H, m including s for CH₃SO₂, 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); \( \delta_C \) (63 MHz, CDCl\(_3\)) 171.2 (CO\(_2\)CH\(_3\)), 155.0, 154.7 (CO\(_2\)-t-Bu), 81.1 (CMe\(_3\)), 75.3, 75.0 (CH-5), 53.7, 52.4 (CH-2), 52.4 (CO\(_2\)Me), 45.8, 44.5 (CH\(_2\)-6), 38.7 (CH\(_3\)SO\(_2\)), 28.2 (CH\(_2\)-4 and CMe\(_3\)), 24.7 (CH\(_2\)-3); MS (ESI): m/z = 360 [M+Na]\(^+\) 100%.

(2S*,5R*)-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); \( \nu_{\text{max}} \) (neat)/cm\(^{-1}\) 2971, 1736, 1692, 1336, 1165, 1147, 902; \( \delta_H \) (250 MHz, CDCl\(_3\); Me\(_4\)Si) 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\(_2\)CH\(_3\)), 3.40–2.90 (4 H, m, CH\(_3\)SO\(_2\), 6-H), 2.25–1.90 (3 H, m, 3-H, 4-H), 1.75–1.30 (10 H, m, 4-H, t-Bu); \( \delta_C \) (63 MHz, CDCl\(_3\)) 170.9, 170.6 (CO\(_2\)CH\(_3\)), 155.0 (CO\(_2\)-t-Bu), 80.4 (CMe\(_3\)), 74.2, 74.1 (CH-5), 53.8, 52.4 (CH-2), 52.0 (CO\(_2\)CH\(_3\)), 45.4, 44.0 (CH\(_2\)-6), 38.3 (CH\(_3\)SO\(_2\)), 27.9 (CMe\(_3\)), 25.6 (CH\(_2\)-4), 20.2 (CH-3); MS (ESI): m/z = 360 [M+Na]\(^+\) 100%.

(2S*,5R*)-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) tosloxy 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\(_2\)O); (Found: C, 51.67; H, 5.68; N, 3.77. C\(_{16}\)H\(_{21}\)NO\(_7\)S requires C, 51.74; H, 5.70; N, 3.77); \( \delta_H \) (250 MHz, CDCl\(_3\); Me\(_4\)Si) 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\(_2\)CH\(_3\)), 3.30–3.00 (1 H, m, 6-H), 2.44 (3 H, s, CH\(_3\)SO\(_2\)), 2.25–1.35 (4 H, m, 3-H, 4-H); \( \delta_C \) (63 MHz, CDCl\(_3\)) 171.7 (CO\(_2\)CH\(_3\)), 156.9 (NCO\(_2\)CH\(_3\)), 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\(_2\)CH\(_3\), CO\(_2\)CH\(_3\)), 45.3, 44.9 (CH\(_2\)-6), 25.6 (CH\(_2\)-4), 21.7 (Ar-CH\(_3\)), 20.5 (CH\(_2\)-3); MS (ESI): m/z = 394 [M+Na]\(^+\) 100%.

(2S*,5S*)-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-tosloxy compound cis-14a as a colourless oil (108 mg, 67%). \( R_f = 0.24 \) (cyclohexane/AcOEt 6:4); \( \delta_H \) (250 MHz, CDCl\(_3\); Me\(_4\)Si) 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\(_2\)CH\(_3\)), 3.05–2.75 (1 H, m, 6-H), 2.43 (3 H, s, CH\(_3\)SO\(_2\)), 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); δC (63 MHz, CDCl3) 170.9 (C\textsubscript{O2CH3}), 156.3, 155.9 (NCO\textsubscript{2CH3}), 145.1 (C\textsubscript{Ar}), 133.9 (C\textsubscript{Ar}), 130.0 (CH\textsubscript{Ar}), 127.7 (CH\textsubscript{Ar}), 75.2 (CH-5), 53.3, 52.9, 52.5 (CH-2, NCO\textsubscript{2CH3}, CO\textsubscript{2CH3}), 45.2, 44.7 (CH\textsubscript{2-6}), 27.7 (CH\textsubscript{2-4}), 25.0, 24.7 (CH\textsubscript{2-3}), 21.7 (CH\textsubscript{3-Ar}); MS (ESI): m/z = 394 [M+Na\textsuperscript{+}] 100%.

(2S*,5R*)-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\textsuperscript{®}, 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\textsubscript{2}O (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\textsubscript{H} (250 MHz, CD\textsubscript{3}OD; Me\textsubscript{4}Si) 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\textsubscript{CO2CH3}), 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); δC (63 MHz, CD\textsubscript{3}OD) 172.6 (C\textsubscript{O2CH3}), 158.6 (NCO\textsubscript{2CH3}), 55.0, 54.8 (CH-2), 54.1, 54.3 (2\textsubscript{CO2CH3}), 46.5 (CH\textsubscript{5}), 44.3, 44.0 (CH\textsubscript{2-6}), 23.9 (CH\textsubscript{2-4}), 20.9 (CH\textsubscript{2-3}); MS (ESI): m/z = 217 [M+H\textsuperscript{+}] 100%.

(2S*,5S*)-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\textsubscript{H} (250 MHz, CD\textsubscript{3}OD; Me\textsubscript{4}Si) 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\textsubscript{CO2CH3}), 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); δC (63 MHz, CD\textsubscript{3}OD) 172.6 (C\textsubscript{O2CH3}), 158.6 (NCO\textsubscript{2CH3}), 54.7, 54.4 (CH-2), 53.9, 53.1 (2\textsubscript{CO2CH3}), 47.9 (CH\textsubscript{5}), 44.7, 44.5 (CH\textsubscript{2-6}), 26.4 (CH\textsubscript{2-4}), 25.9, 25.7 (CH\textsubscript{2-3}); MS (ESI): m/z = 217 [M+H\textsuperscript{+}] 100%.

(2S*,5S*)-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\textsuperscript{®}, 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\textsubscript{H} (250 MHz, CD\textsubscript{3}OD; Me\textsubscript{4}Si) 4.94–4.59 (1 H, m, 2-H), 4.19–3.93 (1 H, m, 6-H), 3.70 (3 H, s, CO\textsubscript{2CH3}), 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, NH), 1.45, 1.42 (9 H, s, CMe₃), 1.15–0.94 (1 H, m, 4-H).

(2S*,5R*)-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; δH (250 MHz, CD3OD; Me4Si) 4.85–4.53 (1 H, m, 2-H), 3.82–3.66 (1 H, m, 6-H), 3.61 (3 H, s, CO2CH3), 3.18–2.92 (2 H, m, 5-H, 6-H), 2.25 (2 H, br s, NH), 2.08–1.82 (2 H, m), 1.55–1.42 (2 H, m), 1.34 (9 H, s, CMe3); δC (63 MHz, CD3CN) 172.1 (CO2CH3), 156.4, (CO2-t-Bu), 80.4 (CMe3), 54.1, 53.5 (CH-2), 52.1 (CO2CH3), 48.2, 47.4 (CH2-6), 44.5 (CH-5), 28.3 (CMe3), 27.6 (CH2-4), 20.4 (CH3-3).

(2S*,5S*)-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 (H2O/MeOH 95:5) afforded the amino compound cis-15’b as a white solid (65 mg, 63%).

ν max(neat)/cm–1 2971, 2971, 2868, 1687, 1625, 1555, 1460, 1444, 1416, 1387, 1364, 1341, 1300, 1289, 1245, 1168, 1160, 1111, 1070, 1052, 1023; δH (250 MHz, D2O) 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, CMe3, 4-H); δC (63 MHz, CD3CN) 177.7 (CO2H), 157.5 (CO2-t-Bu) 81.6 (CMe3), 56.9 (CH-2), 47.4 (CH-5), 42.8 (CH2-6), 28.1, 25.1 (CMe3, CH2-3, CH2-4); MS (ESI): m/z = 245 [M+ H]+ 100%.

(2S*,5R*)-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 (H2O), the amino compound trans-15’b as a white solid (84 mg, 72%).

m.p. = 225–230 °C; δH (250 MHz, D2O) 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, 4-H), 2.00–1.65 (3 H, m, 3-H, 4-H), 1.47 (9 H, s, CMe3); δC (63 MHz, CD3CN) 177.6 (CO2H), 158.2 (NCO2tBu), 81.6 (CMe3), 57.9, 56.6 (CH-2), 47.1 (CH-5), 45.1, 44.2 (CH2-6), 28.8 (CMe3), 24.9 (CH3-3), 22.0 (CH2-3); MS (ESI): m/z = 245 [M+ H]+ 100%.

(2S*,5S*)-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(benzyloxy carbonyl)-$N'$-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: $\delta_H$ (250 MHz, CDCl$_3$; Me$_4$Si) 8.18 (1 H, br s, NH), 7.50–7.20 (10 H, m, HAr.), 5.25–5.00 (4 H, m, 2×OCH$_2$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); $\delta_C$ (63 MHz, CDCl$_3$) 176.4 (CO$_2$H), 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 (CMe$_3$), 68.5, 67.5 (2×OCH$_2$Ph), 53.6, 52.5 (CH-2), 46.8 (CH-5), 45.9 (CH$_2$-6), 28.5 (CMe$_3$), 27.7 (CH$_2$-4), 25.2 (CH$_2$-3); MS (ESI): $m/z$ = 555 [M+H$^+$$]$ 100%.

(2$S$*$,5R$*)-5-$N,N'$-bis(Benzyloxy carbonyl)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(benzyloxy carbonyl)-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; $\delta_H$ (250 MHz, CDCl$_3$; Me$_4$Si) 11.57 (1 H, br s, NHZ), 8.65 (1 H, br s, NH), 7.33–7.10 (10 H, m, HAr.), 5.12–4.67 (5 H, m, 2×OCH$_2$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$_3$); $\delta_C$ (63 MHz, CDCl$_3$) 176.3 (CO$_2$H), 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, 128.1 (CH Ar.), 81.3 (CMe$_3$), 68.4, 67.4 (2×OCH$_2$Ph), 54.3, 53.1 (CH-2), 45.6 (CH$_2$-6), 44.8 (CH-5), 28.3 (CMe$_3$), 25.0 (CH$_2$-4), 21.3 (CH$_2$-3); MS (ESI): $m/z$ = 555 [M+H$^+$$]$ 100%.