From Diketopiperazines to Hydantoins: an Unprecedented Rearrangement

Guilhem Chaubet, Guillaume Cazals, Aurélien Lebrun, Jean Martinez, Isabelle Parrot*

Institut des Biomolécules Max Mousseron IBMM UMR 5247 CNRS-Université Montpellier I-Université Montpellier II, Pl. E. Bataillon, 34095 Montpellier Cedex 5, France.

E-mail: isabelle.parrot@um2.fr

Supporting Information
List of content

1. General information
2. Experimental procedures
   2.1 General experimental procedure for the synthesis of Boc-Xaa-Gly-OEt dipeptides
   2.2 General experimental procedures for the synthesis of cyclo-[Gly-Xaa]
   2.3 General experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa]
3. Protocols and characterization
   3.1 Cyclo-[Gly-Xaa]
   3.2 Bis-Boc cyclo-[Gly-Xaa]
   3.3 Bis-Boc cyclo-[Xaa-Xaa]
   3.4 Mono-Boc cyclo-[Gly-Xaa]
   3.5 Hydantoins
      3.5.1 Valine derivatives
      3.5.2 Glycine-Glycine derivatives
      3.5.3 Isoleucine derivatives
      3.5.4 Phenylalanine derivatives
      3.5.5 Lysine derivatives
      3.5.6 Aspartatic acid derivatives
      3.5.7 Diaminopropionionic acid (Dap) derivatives
      3.5.8 Threonine derivatives
      3.5.9 Alanine derivatives
      3.5.10 Alanine-Alanine derivatives
      3.5.11 Valine-Valine derivatives
      3.5.12 2-Aminoisobutyric acid (Aib) derivatives
      3.5.13 Valine-Phenylalanine derivatives
      3.5.14 α-Methyl-Valine (α-Me-Val) derivatives.
4. NMR Spectra
1. General information

All solvents were dried and freshly distilled before use. Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kieselgel 60 F254 plates. Visualization was accomplished with UV light and exposure either to a 10% solution of ninhydrin in ethanol or to a solution of anisaldehyde in ethanol, acetic acid and sulphuric acid followed by heating. Chromatography columns were performed using Merck-Kieselgel 60 (230–400 mesh). Melting points were recorded on a Buchi 510. Mass spectra were obtained on a Micromass Q-Tof mass spectrometer using electrospray ionization. The high resolution mass spectra (HRMS) were measured with a Waters Synapt G2S spectrometer equipped with positive electrospray source ionization (ESI), using Leu-enkephalin as an internal standard. The capillary voltage was set to 1.2 kV and the sampling cone voltage was set to 30 V. HPLC and LC-MS analyses were performed on a Waters-Enpower Pro (column 50 x 4.6 mm Chromolith SpeedRod RP-18, UV detection). Compounds were either separated using a linear gradient system comprising 0.1% aqueous TFA (solvent A) and acetonitrile containing 0.1% TFA (solvent B) using a constant flow rate of 3mLmin⁻¹ or using a linear gradient system comprising 0.1% aqueous formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B) using a constant flow rate of 3mLmin⁻¹. Preparative HPLC were performed on a Gilson PLC 2020 (column 30 x 100 mm Phenomenex Luna 10u C18(2), UV detection at 214 nm and 254 nm). Compounds were separated using a linear gradient system comprising 0.1% aqueous TFA (solvent A) and acetonitrile containing 0.1% TFA (solvent B) using a constant flow rate of 50mLmin⁻¹ with the detector set at 214 nm and 254 nm (method A).

When preparative HPLC did not provide clean separations (i.e. for enantiomeric mixtures), purifications were performed on a Waters Alliance 2790 (column 4.6 x 250 mm Phenomenex Lux 5u Cellulose-2, UV detection on a Waters PDA 996 at 214 nm and 254 nm). Separation was performed according to the method described for each compound with a system comprising 0.1% aqueous formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B) using a constant flow rate of 1mLmin⁻¹ with the detector set at 214 nm and 254 nm (method B).

The optical rotations were obtained at 20°C on a Perkin Elmer Polarimeter with a Sodium lamp at 589 nm and reported as follows: [α]D²⁰ (C: gdl⁻¹, solvent), with [α] in 10⁻¹ degcm²g⁻¹. NMR spectra were recorded at ambient temperature on Bruker Avance DPX 200 MHz, Bruker Avance 300 MHz, Bruker Avance 400 MHz or Bruker Avance III 600 MHz spectrometers. Chemicals shifts (δ) are reported from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift (δ), multiplicity (s=singlet, d=doublet, t=triplet, sept=septuplet, br=broad, m=multiplet), integration, coupling constants (J: Hz) and assignment. The reported ¹H NMR signals were assigned using standard 2D-NMR techniques.

¹³C NMR data are reported as follows: chemical shift (δ) and assignment. The reported ¹³C NMR signals were assigned using DEPT-135 and HMQC experiments or by direct comparison to the ¹³C NMR spectra of corresponding starting materials.

2. Experimental procedures

2.1 General experimental procedure for the synthesis of Boc-Xaa-Gly-OEt dipeptides

To a solution of Boc-Xaa-OH (1.0 equiv.) in anhydrous DMF were sequentially added H-Gly-OEt.HCl (1.1 equiv.), BOP reagent (1.0 equiv.), and then triethylamine (3.0 equiv.). The reaction mixture was stirred under
argon atmosphere at room temperature for 12 h. EtOAc was then added to the reaction media. The organic layer was sequentially washed with 0.1 N HCl, saturated NaHCO₃ solution, dried over Na₂SO₄ and evaporated to dryness to afford the desired dipeptide in 58–100% yield.

2.2 General experimental procedures for the synthesis of cyclo-[Gly-Xaa]

2.2.1 Pathway A

Boc-Xaa-Gly-OEt dipeptide was dissolved in DMF (1.0 vol.). Water (11.0 vol.) was then added to this solution (a precipitation of the substrate might occur). The reaction media was heated in a microwave oven at 150 °C for 10 min., degassed and heated again at 150 °C for 2.5 h. The reaction mixture was then evaporated to dryness under vacuum. The crude material was triturated in DCM to afford the desired diketopiperazine in 66–97% yield.

2.2.2 Pathway B

Boc-Xaa-Gly-OEt dipeptide was dissolved in DCM and TFA was added to obtain a 50 % TFA solution in DCM. The reaction media was stirred at room temperature for 1 h before being evaporated to dryness. The remaining TFA was co-evaporated with cyclohexane to afford the desired TFA salt in quantitative yield.

The TFA salt of H-Xaa-Gly-OEt was then dissolved in butan-1-ol containing 0.1 M of acetic acid. After addition of N-methylmorpholine (1.0 equiv.), the reaction mixture was irradiated in a microwave oven at 150 °C for 1 h. The reaction media was then evaporated to dryness under vacuum. The crude material was triturated in DCM to afford the desired diketopiperazine in 55–93% yield.

2.3 General experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa]

To a suspension of cyclo-[Gly-Xaa] (1.0 equiv.) in dry DMF was slowly added di-tert-butyl dicarbonate Boc₂O (2.1 equiv.) and DMAP (2.1 equiv.). After stirring at room temperature under argon atmosphere for 1.5 h, the solution was diluted with EtOAc and then washed with 1.0 N KHSO₄ solution. After drying on Na₂SO₄, the solvent was removed under vacuum. A rapid filtration on silica gel (DCM:EtOAc 90:10) afforded the bis-Boc DKP in 19–90% yield.
3. Protocols and characterizations

3.1 cyclo-[Gly-Xaa]

Characterizations of the majority of the DKPs have already been reported in the literature. Obtained data were consistent with the reported ones. Cyclo-[Gly-Gly], cyclo-[Gly-Aib], cyclo-[Ala-Ala] and cyclo-[Val-Val] were commercially available and purchased from Aurora, Bachem or Sigma-Aldrich.

(S)-benzyl ((3,6-dioxopiperazin-2-yl)methyl)carbamate \( (\text{C}_{13}\text{H}_{15}\text{N}_{3}\text{O}_{4}, 277.26 \text{ gmol}^{-1}) \): the cyclodipeptide cyclo-[Gly-Dap(Z)] was synthesized according to the pathway B of the general experimental procedure for the synthesis of cyclo-[Gly-Xaa], starting from Boc-Dap(Z)-Gly-\( \text{OEt} \) (682 mg, 1.61 mmol, 1.0 equiv.), with a 60% yield (m = 268 mg) as a white powder.

\( ^1\text{H NMR (MeOD:DMSO-d}_6 \text{ 2:1, 600 MHz)} \) \( \delta \) 3.38 (dd, 1H, \( J = 14.0 \text{ Hz}, J = 5.4 \text{ Hz, H}_\text{CH(C}_\text{H}_2\text{HNHZ)} \)), 3.70 (d, 1H, \( J = 17.6 \text{ Hz, H}_\text{NH(C}_\text{H}_2\text{CO)} \)), 3.78 (d, 1H, \( J = 17.6 \text{ Hz, H}_\text{NH(C}_\text{H}_2\text{CO)} \)), 3.87 (m, 1H, \( \text{HC}_\text{H}^*\text{CH}_2\text{NHZ}) \)), 4.99 (s, 2H, \( \text{HC}_\text{H}_2\text{Ph}) \)), 7.21-7.28 (H\(_\text{Ar}\)); \( ^{13}\text{C NMR (MeOD:DMSO-d}_6 \text{ 2:1, 150 MHz)} \) \( \delta \) 44.8 (C\( \text{CH}_2\text{HNHZ}) \)), 45.6 (C\( \text{NH(C}_\text{H}_2\text{CO)} \)), 56.8 (C\( \text{CH}_2\text{CH(NHZ)} \)), 67.5 (C\( \text{CH}_2\text{Ph}) \)), 129.2-138.6 (C\(_\text{Ar}\)), 158.7 (C\( \text{CO} \)), 168.3 (C\( \text{CO} \)); HPLC \( r_t = 1.12 \); ESI-MS\(^+\) m/z 278.2; HRMS (TOF ES MS\(^+\)) m/z calculated for \([\text{C}_{13}\text{H}_{15}\text{N}_{3}\text{O}_{4} + \text{Na}^+] \) 300.0956 gmol\(^{-1}\), found 300.0956 gmol\(^{-1}\); m.p. 240 °C.

(S)-3-isopropyl-3-methylpiperazine-2,5-dione \( (\text{C}_{8}\text{H}_{14}\text{N}_{2}\text{O}_{2}, 170.21 \text{ gmol}^{-1}) \): the cyclodipeptide cyclo-[Gly-\( \text{I} \)-Me-Val] was synthesized according to the pathway B of the general experimental procedure for the synthesis of cyclo-[Gly-Xaa], starting from Boc-\( \text{I} \)-Me-Val-Gly-\( \text{OEt} \) (499 mg, 1.58 mmol, 1.0 equiv.), with a 78% yield (m = 208.8 mg) as a white powder.

\( ^1\text{H NMR (DMSO-d}_6 \text{, 300 MHz)} \) \( \delta \) 0.84 (d, 3H, \( J = 6.8 \text{ Hz, H}_\text{CH(CH}_3\text{)} \)), 0.86 (d, 3H, \( J = 7.0 \text{ Hz, H}_\text{CH(CH}_3\text{)} \)), 1.22 (s, 3H, \( \text{H}_\text{CH}_2\text{CH}_3 \)), 1.95 (sept, 1H, \( J = 6.8 \text{ Hz, H}_\text{CH(CH}_3\text{)} \)), 3.68 (dd, 1H, \( J = 17.9 \text{ Hz, J = 2.7 Hz, H}_\text{NH(CH}_2\text{CO)} \)), 3.82 (d, 1H, \( J = 17.8 \text{ Hz, H}_\text{NH(CH}_2\text{CO)} \)), 7.89 (brs, 1H, \( \text{H}_\text{N} \)), 8.08 (brs, 1H, \( \text{H}_\text{N} \)); \( ^{13}\text{C NMR (DMSO-d}_6 \text{, 75 MHz)} \) \( \delta \) 15.9 (C\( \text{CH}_2\text{CH}_3 \)), 17.3 (C\( \text{CH}_2\text{CH}_3 \)), 23.1 (C\( \text{CH}_3\)), 36.5 (C\( \text{CH}_2\text{CH}_3 \)), 44.5 (C\( \text{NH(CH}_2\text{CO)} \)), 60.6 (C\( \text{CH}_2\text{CO}) \)), 165.6 (C\( \text{CO}) \)), 170.0 (C\( \text{CO}) \)); HPLC \( r_t = \) none (injection peak); ESI-MS\(^+\) m/z 171.2; HRMS (TOF ES MS\(^+\)) m/z calculated for \([\text{C}_{8}\text{H}_{14}\text{N}_{2}\text{O}_{2} + \text{H}^+] \) 171.1134 gmol\(^{-1}\), found 171.1134 gmol\(^{-1}\); m.p. >250 °C.
3.2 Bis-Boc cyclo-[Gly-Xaa]

Bis-Boc cyclo-[Gly-Xaa] with Xaa = D-Val, Val, Phe, Ile, Ala, Thr(OBn) and Gly have already been described in the literature. Data we obtained were consistent with the reported ones.

(S)-di-tert-butyl 3-4-((benzoyloxy)carbonylamino)butyl)-2,5-dioxopiperazine-1,4-dicarboxylate 5 \((\text{C}_{26}\text{H}_{37}\text{N}_{3}\text{O}_{8}, 519.59 \text{ gmol}^{-1})\): the activated diketopiperazine bis-Boc cyclo-[Gly-Lys(Z)] 5 was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa], starting from cyclo-[Gly-Lys(Z)] (625 mg, 1.96 mmol, 1.0 equiv.), with a 65\% yield (m = 665.8 mg) as a colourless oil.

\[^1\text{H}\] NMR ((\text{CD}_{3})_{2}\text{CO}, 200 \text{ MHz}) δ 1.35-1.61 (m, 24H, H\text{CH}^*\text{CH}_{2}\text{C}_{2}\text{H}_{2} + \text{H\text{CH}^*\text{CH}_{2}\text{CH}_{2} + \text{H\text{CH}^*\text{CH}_{2}\text{NHZ} + \text{H\text{C\text{(CH}_{3})_{3}}}}}), 3.18 (td, 2H, \text{J} = 6.4 \text{ Hz, H\text{CH}_{2}\text{C\text{(CH}_{3})_{3}}}), 4.41 (d, 1H, \text{J} = 18.2 \text{ Hz, H\text{N\text{CH(\text{CO})}}}), 4.62 (d, 1H, \text{J} = 18.3 \text{ Hz, H\text{N\text{CH(\text{CO})}}}), 4.70 (t, 1H, \text{J} = 7.8 \text{ Hz, H\text{CH(\text{CH}_{2})CH}_{2}\text{(N\text{H\text{Z}})}}), 7.29-7.37 (m, 5H, H\text{Ar}); \[^{13}\text{C}\] NMR ((\text{CD}_{3})_{2}\text{CO}, 75 \text{ MHz}) δ 24.2 (C\text{CH}^*\text{C\text{(CH}_{3})_{3}}), 28.6 (C\text{C\text{(CH}_{3})_{3}}), 30.9 (C\text{CH}^*\text{CH}_{2}\text{C\text{(CH}_{3})_{3}}), 33.1 (C\text{C\text{(CH}_{3})_{3}}), 41.5 (C\text{C\text{(CH}_{3})_{3}}), 49.9 (C\text{CH(\text{CH}_{2})CH}_{2}), 66.9 (C\text{(C\text{H\text{N\text{CH(\text{CO})}}})_{2}}), 84.8 (2C, C\text{C\text{(CH}_{3})_{3}}), 129.1-139.1 (C\text{Ar}), 151.8 (2C, C\text{\text{CO} Boc}), 155.5 (C_{\text{CO lactam}}); \text{HPLC \text{rt} = 2.43 min}; \text{ESI-MS}^+ \text{m/z 520.4}; \text{HRMS (TOF ES MS}^+ \text{m/z calculated for \left[C_{26}\text{H}_{37}\text{N}_{3}\text{O}_{8} + \text{Na}^+\right] 542.2478 \text{ gmol}^{-1}, \text{found 542.2484 \text{ gmol}^{-1}}; \text{R}_f = 0.74 (\text{DCM:EtOAc}; 60:40); \text{[a]}^2_{\text{D}} = +45.0 (C = 2.00, \text{MeOH}).

\text{a: in (CD}_{3})_{2}\text{CO peak}; chemical shift determined by HSQC.

(5)-2-(1,4-bis(tert-butoxycarbonyl)-3,6-dioxopiperazin-2-yl)acetic acid 6 \((\text{C}_{16}\text{H}_{24}\text{N}_{2}\text{O}_{8}, 372.37 \text{ gmol}^{-1})\): to 214 mg (10 wt. %) of 10 \% Pd/C was added a solution of the activated diketopiperazine bis-Boc cyclo-[Gly-Asp(OBn)] (2.14 g, 4.63 mmol) in 30 mL of absolute ethanol. The resulting suspension was stirred 3 h at room temperature under hydrogen atmosphere (1 atm.) before being filtered through a celite pad. The crude reaction mixture was purified on silica gel (DCM:MeOH 95:5). Bis-Boc cyclo-[Gly-Asp(OH)] 6 was isolated with a 52\% yield (m = 887 mg) as a colourless oil.

\[^1\text{H}\] NMR (CDCl\text{3}, 300 \text{ MHz}) δ 1.51 (s, 18H, C\text{C\text{(CH}_{3})_{3}}), 3.05 (dd, 1H, J = 17.9 \text{ Hz, J} = 4.5 \text{ Hz, C\text{CH(\text{CH}_{2})}}), 4.39 (d, 1H, J = 18.3 \text{ Hz, H\text{N\text{CH(\text{CO})}}}), 4.56 (d, 1H, J = 18.3 \text{ Hz, H\text{N\text{CH(\text{CO})}}}), 4.93 (t, 1H, J = 4.2 \text{ Hz, H\text{C\text{(CH}_{2})CH}_{2}}); \[^{13}\text{C}\] NMR (CDCl\text{3}, 75 \text{ MHz}) δ 28.1 (C\text{C\text{(CH}_{3})_{3}}), 36.6 (C\text{CH(\text{CH}_{2})}), 50.0 (C\text{CH(\text{CH}_{2})}), 56.6 (C\text{C\text{(CH}_{2})}), 85.2 (C\text{C\text{(CH}_{3})}), 85.6 (C\text{C\text{(CH}_{3})}), 150.2 (C\text{\text{CO} Boc}), 150.3 (C\text{\text{CO} Boc}), 165.3 (C\text{\text{CO lactam}}), 167.0 (C_{\text{CO lactam}}); \text{HPLC \text{rt} = 1.82 min}; \text{ESI-MS}^+ \text{m/z 520.4}; \text{HRMS (TOF ES MS}^+ \text{m/z calculated for \left[C_{16}\text{H}_{24}\text{N}_{2}\text{O}_{8} + \text{Na}^+\right] 395.1430 \text{ gmol}^{-1}, \text{found 395.1429 \text{ gmol}^{-1}}; \text{R}_f = 0.74 (\text{DCM:EtOAc}; 60:40); \text{[a]}^2_{\text{D}} = +45.0 (C = 2.00, \text{MeOH}).

\text{di-tert-butyl 2,2-dimethyl-3,6-dioxopiperazine-1,4-dicarboxylate (C}_{16}\text{H}_{26}\text{N}_{2}\text{O}_{6}, 342.39 \text{ gmol}^{-1})\): the activated diketopiperazine bis-Boc cyclo-[Gly-Aib] was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa], starting from cyclo-[Gly-Aib] (1.57 g, 11.0 mmol, 1.0 equiv.), with a 34\% yield (m = 1.26 g) as a colourless oil.
\[ ^{1}H\text{ NMR (CDCl}_3, 300 \text{ MHz}) \] δ 1.48 (s, 18H, H\text{C(C}_3\text{H}_3)), 1.60 (s, 6H, H\text{C(C}_3\text{H}_3)), 4.32 (s, 2H, H\text{NCH}_2\text{CO}); 
\[ ^{13}C\text{ NMR (CDCl}_3, 75 \text{ MHz}) \] δ 24.5 (C\text{C(C}_3\text{H}_3)), 27.7 (C\text{C(C}_3\text{H}_3)), 28.0 (C\text{C(C}_3\text{H}_3)), 47.9 (C\text{NCH}_2\text{CO}), 62.0 (C\text{C(C}_3\text{H}_3)), 84.9 (C\text{C(C}_3\text{H}_3)), 85.5 (C\text{C(CH}_3)_2), 150.5 (C\text{C(CH}_3)_2), 151.3 (C\text{C(CH}_3)_2), 165.2 (C\text{C(CH}_3)_2), 168.8 (C\text{C(CH}_3)_2); 
HPLC \text{ r}_t = 2.29 \text{ min}; 
ESI-MS\textsuperscript{+} m/z 365.1 \text{ [M+Na]+}; 
HRMS (TOF ES MS\textsuperscript{+}) m/z calculated for [C\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}_6 + \text{Na} +] 365.1689 gmol\textsuperscript{-1}, found 365.1693 gmol\textsuperscript{-1}; 
R\text{f} = 0.41 (PE:Et\text{_2O}; 80:20).

\[ \text{(S)-di-tert-butyl 3-(((benzoxycarbonyl)amino)methyl)-2,5-dioxopiperazine-1,4-dicarboxylate (C}_{23}\text{H}_{31}\text{N}_3\text{O}_8, 477.51 \text{ gmol}^{-1}) \] was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Dap(Z)] starting from cyclo-[Gly-Dap(Z)] (242 g, 0.873 mmol, 1.0 equiv.), with a 22% yield (m = 93.2 mg) as a colourless oil.

\[ ^{1}H\text{ NMR (CDCl}_3, 400 \text{ MHz}) \] δ 1.46 (s, 9H, H\text{C(C}_3\text{H}_3)), 1.48 (s, 9H, H\text{C(C}_3\text{H}_3)), 3.68 (t, \text{J} = 6.5 \text{ Hz}, H\text{CCH}_2\text{NH}_2), 4.21 (d, \text{J} = 18.3 \text{ Hz}, H\text{CCH}_2\text{CO}), 4.60 (d, \text{J} = 18.3 \text{ Hz}, H\text{CCH}_2\text{CO}), 4.85 (t, \text{J} = 6.5 \text{ Hz}, H\text{CCH}_2\text{NH}_2), 5.04 (s, 2H, H\text{CCH}_2\text{Ph}), 5.52 (t, \text{J} = 6.2 \text{ Hz}, H\text{CCH}_2\text{NH}_2), 7.26-7.32 (m, 5H, H\text{Ar}); 
\[ ^{13}C\text{ NMR (CDCl}_3, 100 \text{ MHz}) \] δ 27.9 (C\text{C(C}_3\text{H}_3)), 28.0 (C\text{C(C}_3\text{H}_3)), 42.4 (C\text{CCH}_2\text{NH}_2), 48.9 (C\text{CCH}_2\text{CO}), 60.3 (C\text{C(CH}_3)_3), 67.3 (C\text{C(CH}_3)_3), 85.2 (C\text{C(CH}_3)_3), 85.3 (C\text{C(CH}_3)_3), 128.3-136.2 (C\text{Ar}), 149.7 (C\text{C(CH}_3)_2), 150.1 (C\text{C(CH}_3)_2), 156.9 (C\text{C(CH}_3)_2), 164.2 (C\text{C(CH}_3)_2), 165.4 (C\text{C(CH}_3)_2); 
HPLC \text{ r}_t = 2.49 \text{ min}; 
ESI-MS\textsuperscript{+} m/z 500.2 \text{ [M+Na]+}; 
HRMS (TOF ES MS\textsuperscript{+}) m/z calculated for [C\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_8 + \text{Na} +] 500.2009 gmol\textsuperscript{-1}, found 500.2013 gmol\textsuperscript{-1}; 
R\text{f} = 0.35 (DCM:Et\text{OAc}; 95:5); 
[\text{[\text{\Lambda})D]_{20}^{20} = +2.0 (C = 2.44, \text{MeOH}).

3.3 Bis-Boc cyclo-[Xaa-Xaa]

Bis-Boc cyclo-[Ala-Ala] has already been described in the literature.\textsuperscript{3} Data we obtained were consistent with the reported ones.

\[ \text{Bis-Boc cyclo-[Val-Val] was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa], starting from cyclo-[Gly-Dap(Z)] (242 g, 0.873 mmol, 1.0 equiv.), with a 22% yield (m = 93.2 mg) as a colourless oil.}

\[ ^{1}H\text{ NMR (CDCl}_3, 200 \text{ MHz}) \] δ 0.96 (d, \text{J} = 6.8 \text{ Hz}, H\text{C(CH}_3)_3), 1.15 (d, \text{J} = 6.8 \text{ Hz}, H\text{C(CH}_3)_3), 1.48 (s, 18H, H\text{C(CH}_3)_3), 1.93 (m, 2H, H\text{C(CH}_3)_3), 4.58 (d, \text{J} = 10.1 \text{ Hz}, H\text{CCH}_2\text{CO}); 
\[ ^{13}C\text{ NMR (CDCl}_3, 75 \text{ MHz}) \] δ 19.5 (C\text{C(CH}_3)_3), 21.0 (C\text{C(CH}_3)_3), 28.0 (C\text{C(CH}_3)_3), 34.1 (C\text{C(CH}_3)_3), 64.9 (C\text{C(CH}_3)_3), 84.7 (C\text{C(CH}_3)_3), 150.9 (C\text{C(CH}_3)_2), 167.1 (C\text{C(CH}_3)_2); 
HPLC \text{ r}_t = 2.77 \text{ min}; 
ESI-MS\textsuperscript{+} m/z 399.2; 
HRMS (TOF ES MS\textsuperscript{+}) m/z calculated for [C\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_6 + \text{Na} +] 421.2315 gmol\textsuperscript{-1}, found 421.2319 gmol\textsuperscript{-1}; 
R\text{f} = 0.35 (DCM:Et\text{OAc}; 95:5); 
[\text{[\text{\Lambda})D]_{20}^{20} = +55.8 (C = 3.53, \text{MeOH}).

S7
(2S,5S)-di-tet-butyl 2-benzyl-5-isopropyl-3,6-dioxopiperazine-1,4-dicarboxylate
(C24H34N2O6, 446.54 gmol⁻¹): the activated diketopiperazine bis-Boc cyclo-[Val-Phe] was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa], starting from cyclo-[Val-Phe] (454.4 mg, 1.84 mmol, 1.0 equiv.), with a 64% yield (m = 526.9 mg) as a colourless oil.

**1H NMR (CDCl₃, 600 MHz)** δ 0.98 (d, 3H, J = 6.9 Hz, H_C(H₃)₃), 1.06 (d, 3H, J = 7.0 Hz, H_C(H₃)₃), 1.30 (s, 9H, H_C(H₃)₃), 1.54 (s, 9H, H_C(H₃)₃), 2.02 (m, 1H, H_C(H₃)₂), 2.97 (d, 1H, J = 14.0 Hz, H_C(H₂)), 3.02 (d, 1H, J = 13.9 Hz, H_C(H₂)), 4.44 (d, 1H, J = 5.6 Hz, H_C(H₃)), 5.02 (s, 1H, H_C(H₂)), 7.18-7.33 (m, 5H, H_Ar);

**13C NMR (CDCl₃, 75 MHz)** δ 18.9 (C_C(H₃)₃), 19.5 (C_C(H₃)₃), 28.3 (C_C(H₃)₃), 30.4 (C_C(H₃)), 38.3 (C_C(H₂)), 61.9 (C_C(H₂)), 69.9 (C_C(H₂)), 81.6 (C_C(H₂)), 84.2 (C_C(H₂)), 128.4-132.0 (C_Ar), 150.0 (2C, C_C(O_Boc)), 155.0 (C_C(O_lactam)), 171.8 (C_C(O_lactam));

**HPLC rₜ = 2.81 min; ESI-MS⁺ m/z 469.3 [M+Na]+; HRMS (TOF ES MS+) m/z calculated for [C24H34N2O6 + Na⁺] 469.2315 gmol⁻¹, found 469.2311 gmol⁻¹; Rf = 0.27 (PE:Et₂O; 90:10); ([α]D)²⁰ = -29.7 (C = 2.29, MeOH).

### 3.4 Mono-Boc cyclo-[Gly-Xaa]

(S)-tet-butyl 3-isopropyl-3-methyl-2,5-dioxopiperazine-1-carboxylate (C13H22N2O4, 270.32 gmol⁻¹): the activated diketopiperazine Boc cyclo-[Gly-α-Me-Val] was synthesized according to the general experimental procedure for the synthesis of bis-Boc cyclo-[Gly-Xaa], starting from cyclo-[Gly-α-Me-Val] (192.1 mg, 1.13 mmol, 1.0 equiv.), with a 34% yield (m = 104.6 mg) as a colourless oil.

**1H NMR (CDCl₃, 400 MHz)** δ 0.94 (d, 3H, J = 6.7 Hz, H_C(H₃)₂), 0.95 (d, 3H, J = 6.8 Hz, H_C(H₃)₂), 1.42 (s, 3H, H_C(H₃)), 1.50 (s, 9H, H_C(H₃)), 2.19 (sept, 1H, J = 6.9 Hz, H_C(H₃)₂), 4.22 (m, 1H, J = 18.0 Hz, H_NH₂), 4.31 (d, 1H, J = 18.0 Hz, H_NH₂), 7.35 (brs, 1H, H_NH₂);

**13C NMR (CDCl₃, 100 MHz)** δ 16.1 (C_C(H₃)₂), 17.7 (C_C(H₃)), 24.0 (C_C(H₃)), 28.1 (C_C(H₃)), 37.5 (C_C(H₂)), 48.3 (C_N(H₂)), 63.6 (C_C(H₂)), 84.7 (C_C(H₂)), 150.8 (C_C(O_Boc)), 166.3 (C_C(O_lactam)), 168.0 (C_C(O_lactam));

**HPLC rₜ = 1.46 min; ESI-MS⁺ m/z 271.1; HRMS (TOF ES MS+) m/z calculated for [C13H22N2O4 + Na⁺] 293.1477 gmol⁻¹, found 293.1481 gmol⁻¹; Rf = 0.47 (DCM:EtOAc; 90:10); ([α]D)²⁰ = -29.7 (C = 2.29, MeOH).

*: the Boc protecting group was confirmed to be located on the indicated nitrogen thanks to a HMBC experiment.
3.5 Hydantoins

3.5.1 Valine derivatives

(S)-2-(3-(tert-butoxycarbonyl)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)acetic acid (S)-8

\[ (\text{C}_{13}\text{H}_{20}\text{N}_{2}\text{O}_{6}, 300.31 \text{ gmol}^{-1}) \]: Compound (S)-8 was described in the manuscript (reference 24).

(R)-2-(3-(tert-butoxycarbonyl)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)acetic acid (R)-8

\[ (\text{C}_{13}\text{H}_{20}\text{N}_{2}\text{O}_{6}, 300.31 \text{ gmol}^{-1}) \]: Compound (R)-8 was synthesized according to the general procedure for the synthesis of hydantoins starting from bis-Boc cyclo-[Gly-(D)-Val] 2. The crude reaction mixture was purified using method B (0% to 100% B in 25 min.) yielding hydantoin (R)-8 with a 62% yield as a colourless oil.

Chiral HPLC \( r_1 = 6.72 \text{ min} \) (see Figure S1); \( [\alpha]_D^{20} = -17.6 \) (\( C = 1.40, \text{MeOH} \)).

Figure S1. HPLC Spectra of the crude reaction mixtures of hydantoin (S)-8 and (R)-8; the peak at 6.42 min. corresponds to Boc-deprotected hydantoin, due to the acidity of the solvents.

After the work-up of the reaction mixture of hydantoin (R)-8, 12% of the remaining starting bis-Boc cyclo-[Gly-(D)-Val] 2 were recovered as a single enantiomer (determined by comparison with pure bis-Boc cyclo-[Gly-(L)-Val] 1 using method B [0% to 100% B in 25 min.]; see Figure S2).
Figure S2: Purity of the recovered bis-Boc cyclo-[Gly-(D)-Val]; A: HPLC spectrum of the recovered starting bis-Boc cyclo-[Gly-(D)-Val] (rt = 18.74 min.); B: HPLC spectrum of enantiopure bis-Boc cyclo-[Gly-(L)-Val] (rt = 18.48 min.); C: Superimposition of spectra A and B.

Performing the rearrangement on a $^{15}$N-labelled analogue of DKP 1, permitted us to validate the proposed mechanism (see Scheme S1).

Scheme S1. Synthesis of the $^{15}$N-labeled analogue of hydantoin (S)-8.
15N-labeled-(S)-2-(3-(tert-butoxycarbonyl)-4-isopropyl-2,5-dioxoimidazolidin-1-yl)acetic acid (15N)-(S)-8 (C_{13}H_{20}N_{15}NO_{6}, 301.30 gmol\(^{-1}\)) : The 15N-labeled analogue of (S)-8 was synthesized according to the general procedure for the synthesis of hydantoins starting from 15N-labeled bis-Boc cyclo-[Gly-(L)-Val]. The crude reaction mixture was purified using method B (0% to 100% B in 25 min.) yielding the 15N-labeled hydantoin with a 60% yield as a colourless oil.

**1H NMR (DMSO-d<sub>6</sub>, 600 MHz)**  δ 0.84 (d, 3H, J = 7.0 Hz, H\(_{\text{CH(C\(_{3}H_{3}\))2}}\)), 1.11 (d, 3H, J = 7.1 Hz, H\(_{\text{CH(C\(_{3}H_{3}\))2}}\)), 1.48 (s, 9H, H\(_{\text{C(C\(_{3}H_{3}\))3}}\)), 2.41 (dsept, 1H, J = 3.3 Hz, J = 7.0 Hz, H\(_{\text{CCH(CH\(_{3}\)2)}}\)), 4.06 (dd, 1H, J = 17.5 Hz, J = 1.0 Hz, H\(_{\text{NCCH(OH)}}\)), 4.45 (d, 1H, J = 3.3 Hz, H\(_{\text{CCH(\text{COOH})}}\)), 4.15 (dd, 1H, J = 17.5 Hz, J = 1.0 Hz, H\(_{\text{NCCH(OH)}}\)), 4.45 (d, 1H, J = 3.3 Hz, H\(_{\text{CCH(\text{COOH})}}\)); **13C NMR (DMSO-d<sub>6</sub>, 150 MHz)**  δ 15.7 (C\(_{\text{CCH(\text{COOH})}}\)), 17.8 (C\(_{\text{CCH(\text{COOH})}}\)), 27.5 (C\(_{\text{CCH(\text{COOH})}}\)), 29.1 (C\(_{\text{CCH(\text{COOH})}}\)), 39.3 (C\(_{\text{CCH(\text{COOH})}}\)), 63.8 (C\(_{\text{CCH(\text{COOH})}}\)), 83.1 (C\(_{\text{CCH(\text{COOH})}}\)), 148.1 (C\(_{\text{CCH(\text{COOH})}}\)), 151.6 (C\(_{\text{CCH(\text{COOH})}}\)), 168.1 (C\(_{\text{CCH(\text{COOH})}}\)), 169.5 (C\(_{\text{CCH(\text{COOH})}}\)); **HPLC r<sub>t</sub> = 1.60 min; Chiral HPLC r<sub>t</sub> = 8.34 min; ESI-MS\(^{+}\) m/z 301.1; HRMS (TOF ES MS\(^{+}\)) m/z calculated for [C_{13}H_{20}N_{15}NO_{6} + Na\(^{+}\)] 324.1189 gmol\(^{-1}\), found 324.1194 gmol\(^{-1}\); [\(\alpha\)]\(_{D}^{20}\) = +10.2 (C = 1.30, MeOH).

As depicted below, a \(^1\)H,\(^{15}\)N-HMBC experiment was performed and proved unambiguously the position of the \(^{15}\)N (see Figure S3). We can observe a strong \(^2\)J coupling with the CH\(_2\) group as well as a low \(^1\)J coupling with the CH\(^*\) and a low \(^4\)J correlation with the CH of the isopropyl group. We could also note a \(W\)-type \(^5\)J coupling with one of the methyl group of the isopropyl.

**Figure S3.** \(^1\)H,\(^{15}\)N-HMBC experiment performed on the \(^{15}\)N-labeled analogue of hydantoin (S)-8.

\(\textit{R}\)-tert-butyl 5-isopropyl-3-(2-methoxy-2-oxoethyl)-2,4-dioxoimidazolidine-1-carboxylate 9 (C_{14}H_{22}N_{2}O_{6}, 314.33 gmol\(^{-1}\)): Compound 9 was described in the manuscript (reference 26).
3.5.2 Glycine-Glycine derivatives

No reaction occurred when reacting bis-Boc cyclo-[Gly-Gly] according to the general procedure for the synthesis of hydantoins, allowing us the recovery of more than 95% of unreacted starting material.

3.5.3 Isoleucine derivatives

2-((S)-3-(tert-butoxycarbonyl)-5-(S)-sec-butyl)-2,5-dioxoimidazolidin-1-yl)acetic acid (5S)-10 (C_{14}H_{22}N_{2}O_{6}, 314.33 g.mol\(^{-1}\)): Compound (5S)-10 was described in the manuscript (reference 27).

2-((S)-3-(tert-butoxycarbonyl)-5-(R)-sec-butyl)-2,5-dioxoimidazolidin-1-yl)acetic acid (5R)-10 (C_{14}H_{22}N_{2}O_{6}, 314.33 g.mol\(^{-1}\)): Diastereoisomer (5R)-10 was obtained along with compound (5S)-10 with a 26% yield after purification.

\(^{1}\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 0.92 (t, 3H, \(J = 7.3\) Hz, H\(_{\text{CH2CH3}}\)), 1.15 (d, 3H, \(J = 7.0\) Hz, H\(_{\text{CH2CH3}}\)), 1.10-1.50 (m, 2H, H\(_{\text{CH2CH3}}\)), 1.56 (s, 9H, H\(_{\text{C(CH3)3}}\)), 2.23 (m, 1H, H\(_{\text{CH2CH3}}\)), 4.27 (d, 1H, \(J = 17.6\) Hz, H\(_{\text{CH2COOH}}\)), 4.32 (d, 1H, \(J = 17.6\) Hz, H\(_{\text{CH2COOH}}\)), 4.44 (d, 1H, \(J = 2.7\) Hz, H\(_{\text{CH2COOH}}\)), 6.66 (brs, 1H, H\(_{\text{CH2COOH}}\)); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 12.3 (C\(_{\text{CH2CH3}}\)), 14.9 (C\(_{\text{CH2CH3}}\)), 23.5 (C\(_{\text{CH2CH3}}\)), 28.1 (C\(_{\text{CH2CH3}}\)), 37.2 (C\(_{\text{CH2CH3}}\)), 39.2 (C\(_{\text{CH2CH3}}\)), 64.4 (C\(_{\text{CH2CO}}\)), 84.9 (C\(_{\text{CH2CO}}\)), 148.7 (C\(_{\text{CH2CO}}\)), 152.0 (C\(_{\text{CH2CO}}\)), 169.9 (C\(_{\text{CH2CO}}\)), 171.0 (C\(_{\text{CH2CO}}\)); HPLC \(rt = \) 2.03 min; Chiral HPLC \(rt = \) 7.19 min; ESI-MS\(^+\) \(m/z\) calculated for \([\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_{6} + \text{Na}^{+}\] 337.1376 g/mol\(^{-1}\), found 337.1377; [\(\alpha\)]\(_D\)\(^{20} = +18.0\) (C = 1.00, MeOH).

Hydantoin (5R)-10 was reacted under the same conditions as the starting bis-Boc DKP (1.6 equiv. solid KOH, anhydrous THF, -15 °C to room temperature, 6 hours) in order to elucidate the epimerization step. After 6 hours of reaction, analysis of the crude reaction mixture proved there was no sign of epimerization (Figure S4, panels A and B). However, we could note the formation of a peak at 7.69 minutes. Analysis of the mass spectrum of this compound proved it was not the epimer (5S)-10 based on the differences between the spectra of these two compounds (Figure S4, panels E and F). On the other hand, mass spectrum of the remaining hydantoin matched very well to the spectrum previously recorded for this compound, confirming it was the same product (Figure S4, panels C and D). Based on this experience, we concluded the epimerization was not occurring on the hydantoins but rather on the open-chain intermediates.
Figure S4. HPLC spectra of a mixture of isomers (5R)-10 and (5S)-10 and of the crude reaction mixture after experience (panels A and B); mass spectra of the peak at 7.38 min. and 7.39 min. recorded in panels A and B respectively (panels C and D); mass spectra of the peak at 7.89 min. and 7.69 min. recorded in panels A and B respectively (panels E and F).
3.5.4 Phenylalanine derivatives

(S)-2-(4-benzyl-3-(tert-butoxycarbonyl)-2,5-dioxoimidazolidin-1-yl)acetic acid (S)-11 (C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>, 348.35 g.mol⁻¹): Compound (S)-11 was synthesized according to the general procedure for the synthesis of hydantoins starting from bis-Boc cyclo-[Gly-Phe] 4. The crude reaction mixture was purified using method B (isochratic elution with 30% B during 30 min.) yielding hydantoin (S)-11 with a 12% yield as a colourless oil.

1H NMR (CDCl₃, 400 MHz) δ 1.58 (s, 9H, H(C(C₃H₃)₃)), 3.30 (dd, 1H, J = 14.1 Hz, J = 2.5 Hz, H(C₃H₃)), 3.44 (dd, 1H, J = 5.9 Hz, H(C₃H₃)), 3.96 (d, 1H, J = 16.9 Hz, H(NCH₂COOH)), 4.05 (d, 1H, J = 17.6 Hz, H(NCH₂COOH)), 4.72 (dd, 1H, J = 2.7 Hz, J = 5.7 Hz, H(C₃H₃)), 7.02-7.29 (m, 5H, HAr);

13C NMR (CDCl₃, 100 MHz) δ 28.2 (CC(C₃H₃)₃), 35.4 (C(C₃H₃)), 39.4 (CN(C₃H₂COOH)), 60.9 (C(C₃H₃)), 85.2 (C(C₃H₃)), 127.9-133.4 (CAr), 148.7 (C(C₃H₃)), 151.5 (C(NCOON)), 167.7 (C(NCOOCH₂)), 169.9 (C(C₃H₂COOH));

ESI-MS+ m/z 349.2; HRMS (TOF ES MS⁺) m/z calculated for [C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub> + Na⁺] 371.1219 gmol⁻¹, found 371.1220 gmol⁻¹; [α]<sub>D</sub> <sup>20</sup> = +6.7 (C = 0.30, MeOH).

5-Benzyl-3-carboxymethyl-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester (R)-11 (C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>, 348.35 g.mol⁻¹): Enantiomer (R)-11 was obtained along with compound (S)-11 with a 12% yield after purification as a colourless oil.

Chiral HPLC r<sub>t</sub> = 21.17 min; [α]<sub>D</sub> <sup>20</sup> = -6.7 (C = 0.30, MeOH).

(S)-2-(3-(tert-butoxycarbonyl)-2,5-dioxoimidazolidin-1-yl)-3-phenylpropanoic acid (S)-15 (C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>, 348.35 g.mol⁻¹): Isomer (S)-15 was obtained along with compound (S)-11 with a 25% yield after purification as a colourless oil.

1H NMR (CDCl₃, 400 MHz) δ 1.50 (s, 9H, H(C(C₃H₃)₃)), 3.49 (m, 2H, H(C₃H₃)), 3.99 (d, 1H, J = 17.9 Hz, H(NCH₂COOH)), 4.10 (d, 1H, J = 17.9 Hz, H(NCH₂COOH)), 5.02 (dd, 1H, J = 10.8 Hz, J = 5.9 Hz, H(NCO)), 7.15-7.27 (m, 5H, HAr);

13C NMR (CDCl₃, 100 MHz) δ 28.1 (C(C₃H₃)), 33.9 (C(C₃H₃)), 48.7 (C(NCOON)), 54.1 (C(NCO)), 85.2 (C(C₃H₃)), 127.4-136.3 (CAr), 148.4 (C(C₃H₃)), 152.0 (C(NCO)), 167.2 (C(NCOCH₂)), 171.8 (C(NCOOCH₂)); HPLC r<sub>t</sub> = 2.06 min; Chiral HPLC r<sub>t</sub> = 23.73 min; ESI-MS+ m/z 349.2; HRMS (TOF ES MS⁺) m/z calculated for [C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub> + Na⁺] 371.1219 gmol⁻¹, found 371.1218 gmol⁻¹; [α]<sub>D</sub> <sup>20</sup> = -12.3 (C = 0.30, MeOH).

(R)-2-(3-(tert-butoxycarbonyl)-2,5-dioxoimidazolidin-1-yl)-3-phenylpropanoic acid (R)-15 (C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>, 348.35 g.mol⁻¹): Isomer (R)-15 was obtained along with compound (S)-11 with a 25% yield after purification as a colourless oil.

Chiral HPLC r<sub>t</sub> = 25.00 min; [α]<sub>D</sub> <sup>20</sup> = +12.3 (C = 0.30, MeOH).
3.5.5 Lysine derivatives

2-(4-((benzyloxy)carbonyl)amino)butyl)-3-(tert-butoxycarbonyl)-2,5-dioxoimidazolidin-1-yl)acetic acid 12 (C_{22}H_{29}N_{3}O_{8}, 463.48 gmol⁻¹):

Compound 12 was synthesized according to the general procedure for the synthesis of hydantoins starting from bis-Boc cyclo-[Gly-Lys(Z)]. The crude reaction mixture was purified using method B (isocratic elution with 45% B during 11 min.) yielding hydantoin 12 with a 52% yield as a colourless oil and as an inseparable mixture of enantiomers.

¹H NMR ((CD₃)₂CO, 400 MHz) δ 1.37-1.45 (m, 2H, H CH*CH₂C₅H₅), 1.49-1.58 (m, 11H, H C(CH₃)₃), 2.11-2.23 (m, 2H, H CH*C₅H₂CH₂), 3.14 (td, 2H, J = 7.0 Hz, J = 1.6 Hz, H CH₂C₅H₂NHZ), 4.20 (d, 1H, J = 17.4 Hz, H NC₅H₂COOH), 4.22 (d, 1H, J = 17.3 Hz, H NC₅H₂COOH), 4.59 (dd, 1H, J = 6.5 Hz, J = 2.9 Hz, H C(CH₃)₃CH₂), 5.04 (s, 2H, HC₅H₂Ph), 7.28-7.36 (m, 5H, H Ar);

¹³C NMR ((CD₃)₂CO, 150 MHz) δ 21.3 (CCH*CH₂C₅H₂), 28.2 (C C(CH₃)₃), 29.4 (2C, C CH*C₅H₂CH₂ + C C₅H₂CH₂NHZ), 40.3 (C CH₂C₅H₂NHZ), 41.3 (C N₅H₂COOH), 60.6 (C C₅H₂Ph), 84.1 (C C(CH₃)₃), 128.6-138.6 (CAr), 149.3 (C C₅H₂O Boc), 152.6 (CN C₅H₂ON), 157.3 (C CO₂Z), 168.8 (C NCOCH₃), 171.5 (C NCH₂COOH);

HPLC rt = 2.00 min; Chiral HPLC rt = 2.93 min; ESI-MS⁺ m/z 464.1; HRMS (TOF ES MS⁺) m/z calculated for [C_{22}H_{29}N_{3}O_{8} + Na⁺] 486.1852 gmol⁻¹, found 486.1857 gmol⁻¹.

6-(((benzyloxy)carbonyl)amino)-2-(3-(tert-butoxycarbonyl)-2,5-dioxoimidazolidin-1-yl)hexanoic acid 16 (C_{22}H_{29}N_{3}O_{8}, 463.48 gmol⁻¹): Compound 16 was obtained along with compound 12 with a 34% yield after purification as a colourless oil and an inseparable mixture of enantiomers.

¹H NMR ((CD₃)₂CO, 400 MHz) δ 1.36 (m, 2H, H CH*CH₂C₅H₂), 1.49-1.60 (m, 11H, H C(CH₃)₃ + HC₅H₂CH₂), 2.15 (m, 2H, H CH*C₅H₂CH₂), 3.12 (t, 2H, J = 6.9 Hz, H CH₂C₅H₂NHZ), 4.34 (d, 1H, J = 17.4 Hz, H NCH₂COOH), 4.39 (d, 1H, J = 17.5 Hz, H NCH₂COOH), 4.63 (t, 1H, J = 7.6 Hz, H CH₂C₅H₂CH₂), 5.04 (s, 2H, H CH₂Ph), 7.27-7.36 (m, 5H, H Ar);

¹³C NMR ((CD₃)₂CO, 150 MHz) δ 25.1 (CCH*CH₂C₅H₂), 31.2 (t, 2H, J = 6.9 Hz, H CH₂C₅H₂NHZ), 4.34 (d, 1H, J = 17.4 Hz, H NCH₂COOH), 4.39 (d, 1H, J = 17.5 Hz, H NCH₂COOH), 4.63 (t, 1H, J = 7.6 Hz, H CH₂C₅H₂CH₂), 5.04 (s, 2H, H CH₂Ph), 7.27-7.36 (m, 5H, H Ar);

HPLC rt = 2.00 min; Chiral HPLC rt = 2.18 min; ESI-MS⁺ m/z 464.1; HRMS (TOF ES MS⁺) m/z calculated for [C_{22}H_{29}N_{3}O_{8} + Na⁺] 486.1852 gmol⁻¹, found 486.1857 gmol⁻¹.

Coupling 12 and 16 with H-Phe-OBn.HCl allowed us to separate and isolate the resulting diastereoisomers 18, 19 and 20 with a 72% yield (see Scheme S2). As expected, coupling of 12 gave 2 distinct products, in a 50:50 ratio. However, coupling of 16 only gave 1 product, urging us to assume that one of the two enantiomers of 16 did not react. Since we have no clue regarding the stereochemistry of the obtained products, no unknown stereogenic centres was attributed.
Scheme S2. Coupling of hydantoins 12 and 16 with H-Phe-OBn.HCl.

5-(4-Benzyloxycarbonylamino-butyl)-3-[(1-benzyloxycarbonyl-2-phenyl-ethylcarbamoyl)-methyl]-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 18 (C_{38}H_{44}N_{4}O_{9}, 700.77 gmol⁻¹): Compound 18 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (30% to 100% B in 15 min.) yielding the coupling product with a 24% overall yield as a colourless oil.

\[
\text{H NMR (CDCl}_3, 600 MHz) \delta 1.36 (m, 2H, HCH*CH}_2C_H2), 1.51 (m, 2H, HC_H2CHNHZ), 1.56 (s, 9H, HC(C_H3)3), 2.03 (m, 1H, HCH*CH}_2C_H2), 2.13 (m, 1H, HCH*CH}_2C_H2), 3.03 (dd, 1H, J = 4.1 Hz, J = 13.7 Hz, HCH*CH}_2C_H2), 3.12 (m, 1H, HCH*CH}_2C_H2), 3.21 (m, 1H, HCH*NH), 4.13 (d, 1H, J = 15.8 Hz, HCH*CO), 4.17 (d, 1H, J = 15.8 Hz, HCH*CO), 4.49 (m, 1H, HCH*CH}_2C_H2), 4.88 (m, 1H, HCH*CH}_2C_H2), 5.07 (brs, 2H, HNHCO2C_H2Ph), 5.10 (d, 1H, J = 12.0 Hz, HCH*CO2C_H2Ph), 5.16 (d, 1H, J = 12.0 Hz, HCH*CO2C_H2Ph), 5.18 (m, 1H, HCH*CO2C_H2Ph), 6.10 (d, 1H, J = 7.4 Hz, HCH*NHCO), 6.93-7.37 (m, 15H, HAr), 13C NMR (CDCl}_3, 150 MHz) δ 20.8 (CCH*CH}_2C_H2), 28.2 (CCH}_2C_H2), 29.4 (2C, CCH}_2C_H2 + CCH}_2C_H2), 37.6 (CCH}_2C_H2), 40.8 (CCH}_2C_H2), 41.2 (CCH}_2C_H2), 53.5 (CCH}_2C_H2), 60.0 (CCH}_2C_H2), 66.7 (CCH}_2C_H2), 67.8 (CCH}_2C_H2), 84.7 (CCH}_2C_H2), 127.3-136.9 (CAr), 148.5 (C_CH2Boc), 151.9 (C_NCO), 156.6 (C_CO z), 164.6 (C_NCO2), 170.7 (C_NCO2), 171.0 (C_CH2Boc), HPLC r_t = 2.89 min; Chiral HPLC r_t = 14.45 min; ESI-MS⁺ m/z 701.4; HRMS (TOF ES MS⁺) m/z calculated for [C_{38}H_{44}N_{4}O_{9} + H⁺] 701.3187 gmol⁻¹, found 701.3193 gmol⁻¹; [α]_D^{20} = +13.9 (C = 0.30, MeOH).

5-(4-Benzyloxycarbonylamino-butyl)-3-[(1-benzyloxycarbonyl-2-phenyl-ethylcarbamoyl)-methyl]-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 19 (C_{39}H_{46}N_{5}O_{9}, 700.77 gmol⁻¹): Compound 19 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (30% to 100% B in 15 min.) yielding the coupling product with a 25% yield as a colourless oil.

\[
\text{H NMR (CDCl}_3, 600 MHz) \delta 1.34 (m, 1H, HCH*CH}_2C_H2), 1.42 (m, 1H, HCH*CH}_2C_H2), 1.51 (m, 2H, HCH*CH}_2C_H2), 1.56 (s, 9H, HCH*CH}_2C_H2), 1.62 (m, 1H, HCH*CH}_2C_H2), 2.03 (m, 1H, HCH*CH}_2C_H2), 2.13 (m, 1H, HCH*CH}_2C_H2), 3.03 (dd, 1H, J = 3.8 Hz, J = 13.7 Hz, HCH*CH}_2C_H2), 3.12 (m, 2H, HCH*CH}_2C_H2), 3.16 (m, 1H, HCH*CH}_2C_H2), 3.21 (m, 1H, HCH*NH), 4.10 (d, 1H, J = 16.0 Hz, HCH*CO), 4.17 (d, 1H, J = 16.0 Hz, HCH*CO), 4.48 (m, 1H, HCH*CH}_2C_H2), 4.88 (m, 1H, HCH*CH}_2C_H2), 5.07 (brs, 2H, HNHCO2C_H2Ph), 5.10 (d, 1H, J = 12.0 Hz, HCH*CO2C_H2Ph), 5.16 (d, 1H, J = 12.0 Hz, HCH*CO2C_H2Ph), 5.18 (m, 1H, HCH*CO2C_H2Ph), 6.10 (d, 1H, J = 7.4 Hz, HCH*NHCO), 6.93-7.37 (m, 15H, HAr), 13C NMR (CDCl}_3, 150 MHz) δ 20.8 (CCH*CH}_2C_H2), 28.2 (CCH}_2C_H2), 29.4 (2C, CCH}_2C_H2 + CCH}_2C_H2), 37.6 (CCH}_2C_H2), 40.8 (CCH}_2C_H2), 41.2 (CCH}_2C_H2), 53.5 (CCH}_2C_H2), 60.0 (CCH}_2C_H2), 66.7 (CCH}_2C_H2), 67.8 (CCH}_2C_H2), 84.7 (CCH}_2C_H2), 127.3-136.9 (CAr), 148.5 (C_CO_t), 151.9 (C_NCO), 156.6 (C_CO z), 164.6 (C_NCO2), 170.7 (C_NCO2), 171.0 (C_CH2Boc), HPLC r_t = 2.89 min; Chiral HPLC r_t = 14.45 min; ESI-MS⁺ m/z 701.4; HRMS (TOF ES MS⁺) m/z calculated for [C_{39}H_{46}N_{5}O_{9} + H⁺] 701.3187 gmol⁻¹, found 701.3193 gmol⁻¹; [α]_D^{20} = +13.9 (C = 0.30, MeOH).
H~N CO2C~H~Ph), 5.10 (d, 1H, J = 12.1 Hz, H~CH~CO2C~H~Ph), 5.16 (d, 1H, J = 12.1 Hz, H~CH~CO2C~H~Ph), 5.22 (t, 1H, J = 5.8 Hz, H~CH~CO2C~H~Ph), 5.10 (d, 1H, J = 7.3 Hz, H~NH~CH~CO), 6.93-7.37 (m, 15H, HAr); ^13C NMR (CDCl~3, 150 MHz) δ 20.5 (C~CH~CH~2), 28.2 (C~CH~CH~2), 29.5 (2C, C~CH~CH~2 + C~CH~CH~2NHz), 37.5 (C~CH~CH~2), 40.8 (C~CH~CH~2), 41.2 (C~NH~CH~2), 53.7 (C~CH~CH~2), 60.0 (C~CH~CH~2), 66.6 (C~NH~CO2C~H~Ph), 67.8 (C~CH~CO2C~H~Ph), 84.8 (C~CH~CH~3), 127.3-136.9 (C~Ar), 148.5 (C~CO~Boc), 151.9 (C~CON), 156.7 (C~CO~Z), 164.6 (C~CONH~CO), 170.9 (C~CO~CH~3), 171.0 (C~CH~CO2Ch); HPLC r~t = 2.89 min; Chiral HPLC r~t = 14.78 min; ESI-MS m/z 701.4; HRMS (TOF ES MS+) m/z calculated for [C~38H~44N~4O~9 + Na+] 723.3006 gmol~1, found 723.3004 gmol~1; [a]~D~20 = +17.5 (C = 0.50, MeOH).

3-[5-Benzoylcarbonylamino-1-(1-benzyloxycarbonyl-2-phenylethylcarbamoyl)-pentyl]-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 20 (C~38H~44N~4O~9, 700.77 gmol~1): Compound 20 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (30% to 100% B in 15 min.) yielding the coupling product with a 15% yield as a colourless oil.

^1H NMR (CDCl~3, 600 MHz) δ 1.24 (m, 2H, H~CH~CH~2), 1.47 (m, 2H, H~CH~CH~2), 1.56 (s, 9H, H~N(C~H~3))), 1.95 (m, 1H, H~CH~CH~2), 2.19 (m, 1H, H~CH~CH~2), 3.06 (dd, 1H, J = 14.0 Hz, J = 6.4 Hz, H~CH~CH~2), 3.14 (m, 1H, H~CH~CH~2NHz), 3.17 (dd, 1H, J = 14.0 Hz, J = 5.8 Hz, H~CH~CH~2), 4.12 (d, 1H, J = 18.0 Hz, H~NH~CO2C~H~Ph), 4.17 (d, 1H, J = 18.0 Hz, H~NH~CO2C~H~Ph), 4.54 (dd, 1H, J = 5.9 Hz, J = 10.1 Hz, H~CH~CH~2), 4.74 (t, 1H, J = 5.6 Hz, H~CH~CH~2NHz), 4.87 (dt, 1H, J = 7.3 Hz, J = 6.4 Hz, H~CH~CH~2), 5.08 (brs, 2H, H~NH~CO2C~H~Ph), 5.10 (d, 1H, J = 12.1 Hz, H~CH~CO2C~H~Ph), 5.18 (d, 1H, J = 12.1 Hz, H~CH~CO2C~H~Ph), 6.54 (d, 1H, J = 7.3 Hz, H~NH~CH~CO), 7.00-7.35 (m, 15H, HAr); ^13C NMR (CDCl~3, 150 MHz) δ 23.5 (C~CH~CH~2), 28.1 (C~CH~CH~2), 27.6 (C~CH~CH~2), 37.6 (C~CH~CH~2), 40.5 (C~CH~CH~2), 48.5 (C~CO2C~H~Ph), 53.6 (C~CH~CH~2), 55.7 (C~CH~CH~2), 66.6 (C~NH~CO2C~H~Ph), 67.6 (C~CH~CO2C~H~Ph), 84.9 (C~CH~CH~3), 127.2-136.7 (C~Ar), 148.2 (C~CO~Boc), 151.8 (C~CON), 156.6 (C~CO~Z), 167.6 (C~CONH~CO), 167.8 (C~CO~CH~3), 171.1 (C~CH~CO2Ch); HPLC r~t = 2.89 min; Chiral HPLC r~t = 13.68 min; ESI-MS m/z 701.4; HRMS (TOF ES MS+) m/z calculated for [C~38H~44N~4O~9 + H+] 701.3187 gmol~1, found 701.3192 gmol~1; [a]~D~20 = -10.7 (C = 0.60, MeOH).
3.5.6 Aspartatic acid derivatives

Performing the rearrangement on the bis-Boc cyclo-[Gly-Asp(Obn)] gave 73% of conversion into a multitude of side-products, mainly saponification and ring-opening products of both DKP and hydantoin. Performing the rearrangement on the bis-Boc cyclo-[Gly-Asp(OH)] allowed isolation of the expected hydantoin 2g.

![Diagram of 2,2'-((3-(tert-butoxycarbonyl)-2,5-dioxoidazolidine-1,4-diyl)diacetic acid 13](image)

\(\text{2,2'}-(3-(\text{tert-butoxycarbonyl})-2,5\text{-dioximidazolidine-1,4-diyl)}\text{diacetic acid 13} \)  
(C\(_{12}\)H\(_{16}\)N\(_2\)O\(_8\), 316.26 g.mol\(^{-1}\)): Compound 13 was synthesized according to the general procedure for the synthesis of hydantoin starting from bis-Boc cyclo-[Gly-Asp(OH)]. The crude reaction mixture was purified using method B (isocratic elution with 30% B during 25 min.) yielding hydantoin 13 with a 49% yield as a colourless oil.

\(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) 1.47 (s, 9H, H\(_{\text{C(CH\(_3\)}}\)), 2.67 (dd, 1H, \(J = 16.6\) Hz, \(J = 5.2\) Hz, H\(_{\text{C(\text{Ipc\(_{\text{H}}})}}\)), 3.08 (dd, 1H, \(J = 16.6\) Hz, \(J = 8.7\) Hz, H\(_{\text{C(\text{Ipc\(_{\text{H}}})}}\)), 4.28 (d, 1H, \(J = 17.5\) Hz, H\(_{\text{N(\text{CCH\(_3\)}}\text{OOh})}}\)), 4.35 (d, 1H, \(J = 17.4\) Hz, H\(_{\text{N(\text{CCH\(_3\)}}\text{OOh})}}\)), 4.84 (dd, 1H, \(J = 8.2\) Hz, \(J = 5.4\) Hz, H\(_{\text{N(\text{CCH\(_3\)}}\text{OOh})}}\)), 27.6 (C\(_{\text{C(CH\(_3\)}}\)), 34.0 (C\(_{\text{C(CH\(_3\)}}\)), 48.5 (C\(_{\text{C(CH\(_3\)}}\)), 48.6 (C\(_{\text{N(\text{CCH\(_3\)}}\text{OOh})}}\)), 83.0 (C\(_{\text{C(CH\(_3\)}}\)), 148.0 (C\(_{\text{C(\text{Ipc\(_{\text{H}}})}}\)), 151.2 (C\(_{\text{N(\text{CON})}}\)), 167.5 (C\(_{\text{N(\text{CON})}}\)), 169.4 (C\(_{\text{N(\text{CON})}}\)), 171.5 (C\(_{\text{C(CH\(_3\)}}\text{OOh})}}\)); HPLC \(t_r = 1.10\) min; Chiral HPLC \(t_r = 22.82\) min; ESI-MS\(^+\) m/z 317.1; HRMS (TOF ES MS\(^+\)) m/z calculated for [C\(_{12}\)H\(_{16}\)N\(_2\)O\(_8\) + Na\(^+\)] 339.0804 g mol\(^{-1}\), found 339.0805 g mol\(^{-1}\).

3.5.7 Diaminopropionic acid (Dap) derivatives

Performing the rearrangement on the bis-Boc cyclo-[Gly-Dap(Z)] gave quantitative conversion into a multitude of side-products, with no sign of the expected hydantoin in LC-MS.
3.5.8 Threonine derivatives

5-(1-Benzyloxy-ethyl)-3-carboxymethyl-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester (5S,15R)-14 (C_{19}H_{24}N_{2}O_{7}, 392.40 g.mol^{-1}): Compound (5S,15R)-14 was synthesized according to the general procedure for the synthesis of hydantoins. The crude reaction mixture was purified using method B (30% to 75% B in 10 min.), allowing isolation of 2 ring-opening products described hereafter and of an inseparable mixture of isomers (5S,15R)-14, (5R,15R)-14, (9S,10R)-17 and (9R,10R)-17 with a 40% yield. The unexpected ratio of products 14 and 17 we observed could be explained by a ion-dipole interaction (see Figure S5).

Coupling those compounds with H-Phe-OBn.HCl was performed according to the general procedure for the synthesis of dipeptides with a quantitative yield and allowed us to separate the resulting diastereoisomers 21-24 (see Scheme S3). However, Compound 21 was the only product obtained in sufficient quantity to allow full characterization. The three others diastereoisomers were only characterized by ^1H NMR and HRMS.

Scheme S3. Coupling of hydantoins 14 and 17 with H-Phe-OBn.HCl ((5S,15R)-21, (5R,15R)-22, (9S,10R)-23 and (9R,10R)-24).

3-[2-Benzoxyl-1-(1-benzyloxycarbonyl-2-phenyl-ethylcarbamoyl)-propyl]-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 21 (C_{35}H_{39}N_{3}O_{8}, 629.70 g.mol^{-1}): Compound 21 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method A (0% to 60% B in 25 min., then 60%
to 80% B in 25 min.) yielding the coupling product with a 26% overall yield as a colourless oil.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.15 (d, 3H, \(J = 5.9\) Hz, H\(_{\text{CH}}\)), 1.54 (s, 9H, H\(_{\text{C(OCH}_2\text{)}}\)), 3.03 (dd, 1H, \(J = 13.9\) Hz, \(J = 4.6\) Hz, H\(_{\text{CH(CPH)}}\)), 3.13 (dd, 1H, \(J = 14.0\) Hz, \(J = 6.4\) Hz, H\(_{\text{CH(CPH)}}\)), 3.92 (d, 1H, \(J = 11.2\) Hz, H\(_{\text{CH(CCH)}}\)), 4.27 (s, 2H, H\(_{\text{CH(OCH)}}\)), 4.33 (d, 1H, \(J = 11.2\) Hz, H\(_{\text{NCOCO}}\)), 4.45 (dq, 1H, \(J = 9.7\) Hz, \(J = 6.4\) Hz, H\(_{\text{CH(CCH)}}\)), 4.56 (d, 1H, \(J = 9.7\) Hz, H\(_{\text{NCOCO}}\)), 4.79 (dd, 1H, \(J = 7.0\) Hz, \(J = 6.4\) Hz, \(J = 4.6\) Hz, H\(_{\text{CH(CPH)}}\)), 4.93 (d, 1H, \(J = 12.0\) Hz, H\(_{\text{COCH}}\)), 5.13 (d, 1H, \(J = 12.0\) Hz, H\(_{\text{COCH}}\)), 6.98-7.32 (m, 15H, H\(_{\text{Ar}}\)), 7.79 (d, 1H, \(J = 7.0\) Hz, H\(_{\text{Ar}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 17.3 (C\(_{\text{C(CH)}}\)), 28.2 (C\(_{\text{C(CH)}}\)), 37.3 (C\(_{\text{C(CH)}}\)), 49.0 (C\(_{\text{NCOCO}}\)), 53.9 (C\(_{\text{CH(CPH)}}\)), 57.6 (C\(_{\text{NCOCO}}\)), 67.5 (C\(_{\text{COCH}}\)), 70.9 (C\(_{\text{C(CH)}}\)), 73.3 (C\(_{\text{CH(OCH)}}\)), 84.8 (C\(_{\text{C(CH)}}\)), 127.2-137.1 (C\(_{\text{Ar}}\)), 148.4 (C\(_{\text{CO CH}_{3}}\)), 152.0 (C\(_{\text{NCOCO}}\)), 166.1 (C\(_{\text{NCOCO}}\)), 167.9 (C\(_{\text{NCOCO}}\)), 170.7 (C\(_{\text{COCH}}\)); HPLC \(t_r = 3.3\) min; ESI-MS\(^{+}\) \(m/z\) 630.3; HRMS (TOF ES MS\(^{+}\)) \(m/z\) calculated for [C\(_{35}\text{H}_{39}\text{N}_3\text{O}_8 + \text{Na}\)]\(^+\) 652.2635 gmol\(^{-1}\), found 652.2643 gmol\(^{-1}\); \([\alpha]_D^{20} = +13.8\) (C = 0.30, MeOH).

3-[2-Benzoyloxy-1-(1-benzyloxy carbonyl-2-phenyl-ethyl carbamoyl)-propyl]-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 22 (C\(_{35}\text{H}_{39}\text{N}_3\text{O}_8\), 629.70 gmol\(^{-1}\)): Compound 22 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (50% to 100% B in 8 min.) yielding the coupling product with a 8% overall yield as a colourless oil.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.15 (d, 3H, \(J = 6.1\) Hz, H\(_{\text{CH}}\)), 1.54 (s, 9H, H\(_{\text{C(OCH}_2\text{)}}\)), 2.98 (dd, 1H, \(J = 13.8\) Hz, \(J = 7.9\) Hz, H\(_{\text{CH(CPH)}}\)), 3.18 (dd, 1H, \(J = 14.0\) Hz, \(J = 5.4\) Hz, H\(_{\text{CH(CPH)}}\)), 3.82 (d, 1H, \(J = 17.9\) Hz, H\(_{\text{CH(CPH)}}\)), 3.87 (d, 1H, \(J = 17.9\) Hz, H\(_{\text{CH(CPH)}}\)), 4.16 (dq, 1H, \(J = 8.8\) Hz, \(J = 6.1\) Hz, H\(_{\text{CH(CCH)}}\)), 4.26 (d, 1H, \(J = 11.7\) Hz, H\(_{\text{NCOCO}}\)), 4.54 (d, 1H, \(J = 11.7\) Hz, H\(_{\text{NCOCO}}\)), 4.54 (d, 1H, \(J = 8.8\) Hz, H\(_{\text{NCOCO}}\)), 4.85 (dd, 1H, \(J = 7.9\) Hz, \(J = 7.4\) Hz, \(J = 5.4\) Hz, H\(_{\text{CH(CPH)}}\)), 5.05 (d, 1H, \(J = 12.1\) Hz, H\(_{\text{COCH}}\)), 5.17 (d, 1H, \(J = 12.1\) Hz, H\(_{\text{COCH}}\)), 7.02-7.32 (m, 16H, H\(_{\text{Ar}}\) + H\(_{\text{Ar}}\)); HPLC \(t_r = 3.20\) min; Chiral HPLC \(t_r = 8.26\) min; ESI-MS\(^{+}\) \(m/z\) 630.3; HRMS (TOF ES MS\(^{+}\)) \(m/z\) calculated for [C\(_{35}\text{H}_{39}\text{N}_3\text{O}_8 + \text{Na}\)]\(^+\) 652.2635 gmol\(^{-1}\), found 652.2637 gmol\(^{-1}\).

3-[(1-Benzoyloxy carbonyl-2-phenyl-ethyl carbamoyl)-methyl]-5-(1-benzoyloxy-ethyl)-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 23 (C\(_{35}\text{H}_{39}\text{N}_3\text{O}_8\), 629.70 gmol\(^{-1}\)): Compound 23 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (50% to 100% B in 8 min.) yielding the coupling product with a 4% overall yield as a colourless oil.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.39 (d, 3H, \(J = 6.6\) Hz, H\(_{\text{CH}}\)), 1.44 (s, 9H, H\(_{\text{C(OCH}_2\text{)}}\)), 2.94 (dd, 1H, \(J = 13.8\) Hz, \(J = 5.7\) Hz, H\(_{\text{CH(CPH)}}\)), 3.02 (dd, 1H, \(J = 13.8\) Hz, \(J = 6.1\) Hz, H\(_{\text{CH(CPH)}}\)), 4.10 (qd, 1H, \(J = 6.6\) Hz, \(J = 1.9\) Hz, H\(_{\text{CH(CCH)}}\)), 4.15 (d, 1H, \(J = 16.5\) Hz, H\(_{\text{NCOCO}}\)), 4.23 (d, 1H, \(J = 16.5\) Hz, H\(_{\text{NCOCO}}\)), 4.26 (d, 1H, \(J = 12.6\) Hz, H\(_{\text{CH(CPH)}}\)), 4.29 (d, 1H, \(J = 1.9\) Hz, H\(_{\text{NCOCO}}\)), 4.40 (d, 1H, \(J = 12.6\) Hz, H\(_{\text{CH(CPH)}}\)), 4.72 (m, 1H, H\(_{\text{CH(CPH)}}\)), 5.07 (d, 1H, \(J = 12.1\) Hz, H\(_{\text{COCH}}\)), 5.14 (d, 1H, \(J = 12.1\) Hz, H\(_{\text{COCH}}\)), 6.47 (d, 1H, \(J = 7.8\) Hz, H\(_{\text{Ar}}\)), 6.93-7.36 (m, 15H, H\(_{\text{Ar}}\)); HPLC \(t_r = 3.20\) min; Chiral HPLC \(t_r = 9.07\) min; ESI-MS\(^{+}\) \(m/z\) 630.3; HRMS (TOF ES MS\(^{+}\)) \(m/z\) calculated for [C\(_{35}\text{H}_{39}\text{N}_3\text{O}_8 + \text{Na}\)]\(^+\) 652.2635 gmol\(^{-1}\), found 652.2645 gmol\(^{-1}\).
3-[(1-Benzylxycarbonyl-2-phenyl-ethylcarbamoyl)-methyl]-5-(1-benzyloxy-ethyl)-2,4-dioxo-imidazolidine-1-carboxylic acid tert-butyl ester 24 (C_{35}H_{39}N_{3}O_{8}, 629.70 gmol^{-1}): Compound 24 was synthesized according to the general procedure for the synthesis of dipeptides. The crude reaction mixture was purified using method B (50% to 100% B in 8 min.) yielding the coupling product with a 2% overall yield as a colourless oil. 

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.24 (d, 3H, $J = 6.5$ Hz, H$_{CH^*C\text{H}_3}$), 1.51 (s, 9H, H$_{C(CH_3)_3}$), 3.09 (dd, 1H, $J = 13.9$ Hz, $J = 5.2$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 3.10 (dd, 1H, $J = 13.9$ Hz, $J = 5.6$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 4.03 (d, 1H, $J = 16.0$ Hz, H$_{NCH\text{CO}}$), 4.12 (m, 1H, H$_{C\text{H}*CH_3}$), 4.17 (d, 1H, $J = 16.1$ Hz, H$_{NCH\text{CO}}$), 4.49 (d, 1H, $J = 12.0$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 4.57 (d, 1H, $J = 12.0$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 4.62 (d, 1H, $J = 3.1$ Hz, H$_{NCH\text{CO}}$), 4.84 (ddd, 1H, $J = 7.4$ Hz, $J = 5.6$ Hz, $J = 5.2$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 5.10 (d, 1H, $J = 12.1$ Hz, H$_{CO_2\text{C\text{H}_2\text{Ph}}}$), 5.16 (d, 1H, $J = 12.1$ Hz, H$_{CO_2\text{C\text{H}_2\text{Ph}}}$), 6.18 (d, 1H, $J = 7.4$ Hz, H$_{N}$), 6.54-7.35 (m, 15H, H$_{Ar}$); HPLC $r_t$ = 3.20 min; Chiral HPLC $r_t$ = 8.76 min; ESI-MS$^+$ m/z 630.3; HRMS (TOF ES MS$^+$) m/z calculated for [C$_{35}$H$_{39}$N$_3$O$_8$ + H$^+$] 630.2815 gmol$^{-1}$, found 630.2810 gmol$^{-1}$. 

Opening products of hydantoin 17 were also isolated along with the mixture of hydantoins 14 and 17 (see Scheme S4).

Scheme S4. Hydantoin ring opening leading to urea-dipeptides 25 and 26 (25, R = H; 26, R = t-Bu).

3-Benzylxycarbonyl-3-carboxymethyl-3-(tert-Butoxycarbonyl)-ureido]-butyric acid 25 (C$_{19}$H$_{26}$N$_2$O$_8$, 410.42 g.mol$^{-1}$): Ring-opening compound 25 was obtained along with hydantoins 14 and 17 with a 18% yield after purification as a colourless oil.

$^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 1.32 (d, 3H, $J = 6.3$ Hz, H$_{CH^*C\text{H}_3}$), 1.52 (s, 9H, H$_{C(CH_3)_3}$), 4.24 (dq, 1H, $J = 6.3$ Hz, $J = 2.8$ Hz, H$_{CH(C\text{H}_2\text{Ph})}$), 4.44 (d, 1H, $J = 7.8$ Hz, $J = 2.5$ Hz, H$_{NCH\text{CO}}$), 4.45 (d, 1H, $J = 18.0$ Hz, H$_{NCH\text{CO}}$), 4.55 (d, 1H, $J = 11.9$ Hz, H$_{CH_2\text{Ph}}$), 4.57 (d, 1H, $J = 18.0$ Hz, H$_{NCH\text{CO}}$), 4.65 (d, 1H, $J = 7.29$-7.35 (m, 5H, H$_{Ar}$), 7.35 (d, 1H, $J = 7.8$ Hz, H$_{Ar}$); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 17.0 (C$_{CH_2\text{Ph}}$), 28.1 (C$_{CH_3\text{Ph}}$), 45.6 (C$_{NCH_2\text{CO}}$), 59.0 (C$_{CH_2\text{Ph}}$), 71.2 (C$_{CH_2\text{Ph}}$), 73.5 (C$_{CH_2\text{Ph}}$), 85.1 (C$_{CH_3\text{Ph}}$), 127.9-137.9 (C$_{Ar}$), 153.8 (C$_{CO\text{Boc}}$), 155.9 (C$_{NCH_2\text{CO}}$), 174.0 (C$_{NCH_2\text{CO}}$), 174.9 (C$_{CH_2\text{COOH}}$); HPLC $r_t$ = 2.10 min; Chiral HPLC $r_t$ = 15.04 min; ESI-MS$^+$ m/z 411.2; HRMS (TOF ES MS$^+$) m/z calculated for [C$_{19}$H$_{26}$N$_2$O$_8$ + Na$^+$] 433.1587 gmol$^{-1}$, found 433.1581 gmol$^{-1}$; $[\alpha]_D^{20}$ = +26.6 (C = 0.40, MeOH).
3-Benzyl oxy-2-[3-tert-butoxycarbonylmethyl-3-(tert-Butoxycarbonyl)-ureido]-butyric acid 26 (C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>8</sub>, 466.52 g mol<sup>-1</sup>): Ring-opening compound 26 was obtained along with hydantoins 14 and 17 with a 7% yield after purification as a colourless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 1.23 (d, 3H, J = 6.5 Hz, H<sub>CH*C</sub>H<sub>3</sub>), 1.45-1.51 (s, 18H, H<sub>t-Bu</sub>), 4.28 (dq, 1H, J = 6.5 Hz, J = 2.6 Hz, H<sub>CH*C</sub>H<sub>3</sub>), 4.33 (s, 2H, H<sub>CH*CO2tBu</sub>), 4.55 (d, 1H, J = 11.5 Hz, H<sub>CH*NH</sub>), 4.65 (d, 1H, J = 11.5 Hz, H<sub>CH*NH</sub>), 4.71 (dd, 1H, J = 7.8 Hz, J = 2.6 Hz, H<sub>CH*NH</sub>), 6.62 (d, 1H, J = 7.8 Hz, H<sub>CH*NH</sub>), 7.31-7.36 (m, 5H, H<sub>A</sub>r);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz) δ 16.0 (C<sub>CH*C</sub>H<sub>3</sub>), 28.1 (2C, C<sub>CH*(CH<sub>3</sub>)</sub>), 49.3 (C<sub>CH*CO2tBu</sub>), 56.3 (C<sub>CH*NH</sub>), 71.7 (C<sub>CH*CH<sub>3</sub></sub>), 73.9 (C<sub>CH*CH<sub>3</sub></sub>), 83.8 (2C, C<sub>CH*CH<sub>3</sub></sub>), 128.0-137.4 (C<sub>A</sub>r), 152.2 (C<sub>CO2tBu</sub>), 152.3 (C<sub>NH</sub>), 169.5 (C<sub>CH*CO2tBu</sub>), 171.7 (C<sub>CH*CO2tBu</sub>); HPLC t<sub>r</sub> = 2.14 min; Chiral HPLC t<sub>r</sub> = 17.56 min; ESI-MS<sup>+</sup> m/z 489.3 (Na<sup>+</sup> adduct); HRMS (TOF ES MS<sup>+</sup>) m/z calculated for [C<sub>23</sub>H<sub>34</sub>N<sub>2</sub>O<sub>8</sub> + Na<sup>+</sup>] 489.2213 g mol<sup>-1</sup>, found 489.2212 g mol<sup>-1</sup>; [α]<sub>D</sub><sup>20</sup> = +20.0 (C = 0.20, MeOH).

3.5.9 Alanine derivatives

Performing the rearrangement on the bis-Boc cyclo-[Gly-Ala] only gave less than 5% of conversion into the 4 isomers of hydantoins a and b along with their hydrolysed analogues as an inseparable mixture (see Figure S6).

Figure S6. Part of the HPLC spectrum of the crude reaction mixture showing the different compounds.

The recovered starting material showed however no sign of racemization (see Figure S7).
3.5.10 Alanine-Alanine derivatives

Performing the rearrangement on the bis-Boc cyclo-[Ala-Ala] gave 62% of conversion into the 4 diastereoisomers of the hydantoin along with their hydrolysed analogues as an inseparable mixture (see Scheme S5).

Scheme S5. DKP-hydantoin rearrangement on bis-Boc cyclo-[Ala-Ala]

3.5.11 Valine-Valine derivatives

3-tert-Butoxycarbonylamino-3,5-diisopropyl-2,4-dioxo-pyrrolidine-1-carboxylic acid tert-butyl ester 27 (C$_{20}$H$_{34}$N$_2$O$_6$, 398.49 g.mol$^{-1}$): TRAL products 27 were obtained as an inseparable mixture of diastereoisomers [(3R)27 : (3S)27, 1:0.32; de = 52%] when bis-Boc cyclo-[Val-Val] was reacted according to the general procedure for the synthesis of hydantoins. The crude reaction mixture was purified using method B (0 to 100% B in 25 min.) yielding compounds 27 with a 62% yield as a colourless oil.

$^1$H NMR (CDCl$_3$, 600 MHz) δ 0.93 (d, 1H, $J = 7.1$ Hz, H$_{C\text{H}(CH_3)}$), 0.98 (d, 3H, $J = 6.9$ Hz, H$_{C\text{H}(CH_3)}$), 1.02 (d, 3H, $J = 6.9$ Hz, H$_{C\text{H}(CH_3)}$), 1.06 (d, 1H, $J = 6.7$ Hz, H$_{C\text{H}(CH_3)}$), 1.14 (m, 3H + 1H, H$_{C\text{H}(CH_3)}$), 1.16 (m, 3H + 1H, H$_{C\text{H}(CH_3)}$), 1.32 (s, 9H, H$_{C\text{H}(CH_3)}$), 1.36 (s, 9H, H$_{C\text{H}(CH_3)}$), 1.56 (s, 11H + 2.9H, H$_{C\text{H}(CH_3)}$), 1.36 (m, 1H + 0.3H + 0.3H, H$_{C\text{H}(CH_3)}$ + H$_{C\text{H}(CH_3)}$), 1.38 (m, 1H, H$_{C\text{H}(CH_3)}$), 4.14 (d, 0.3H, $J = 7.2$ Hz, H$_{C\text{H}(CH_3)}$), 4.38 (d, 1H, $J = 5.8$ Hz, H$_{C\text{H}(CH_3)}$), 5.03 (s, 1H, H$_{NH}$), 5.36 (s, 0.3H, H$_{NH}$); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 20.3 (C$_{CH_3}$), 28.0 (C$_{CH_3}$), 31.1 (C$_{CH_3}$), 36.1 (C$_{CH_3}$), 41.1 (C$_{CH_3}$), 52.7 (C$_{CH_3}$), 66.0 (C$_{CH_3}$), 129.7 (C$_{CH_3}$), 133.0 (C$_{CH_3}$), 154.2 (C$_{CH_3}$), 173.1 (C$_{CO}$), 173.5 (C$_{CO}$).
150 MHz) δ 15.7 (C-CHeCH3), 16.2 (C-CHeCH3), 16.8 (2C, C-CHeCH3), 18.9 (C-CHeCH3), 19.2 (C-CHeCH3), 19.7 (C-CHeCH3), 19.9 (C-CHeCH3), 28.2 (2C, C-CHeCH3), 28.4 (2C, C-CHeCH3), 30.1 (C-CHeCH3), 30.8 (C-CHeCH3), 31.2 (C-CHeCH3), 31.7 (C-CHeCH3), 65.3 (C-CHeCH3), 66.6 (C-CHeCH3), 69.3 (C-CHeCH3), 69.6 (C-CHeCH3), 81.6 (C-CHeCH3), 84.2 (C-CHeCH3), 84.4 (C-CHeCH3), 150.3 (C-CHeCH3), 150.4 (C-CHeCH3), 155.1 (C-CHeCH3), 155.5 (C-CHeCH3), 171.7 (2C, C-CHeCH3), 205.3 (C-CHeCH3), 205.5 (C-CHeCH3); HPLC rt = 2.64 min; Chiral HPLC rt = 17.56 min; ESI-MS m/z = 421.2 (Na+ adduct); HRMS (TOF ES MS+) m/z calculated for [C20H34N2O6 + Na+] 421.2315 gmol⁻¹, found 421.2319 gmol⁻¹.

3.5.12 2-Aminoisobutyric acid (Aib) derivatives

4-tert-Butoxycarbonylamino-3-hydroxy-2,2-dimethyl-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-buty 1.35 (s, 6H, H3C(CH3)); 1.41 (s, 18H, H3C(CH3)); 4.07 (s, 2H, H3C(CH3)); 8.09 (s, 1H, H3C(CH3)); 13C NMR (CDCl3, 600 MHz) δ 24.9 (C-CHeCH3), 27.5 (C-CHeCH3), 47.6 (C-CHeCH3), 54.8 (C-CHeCH3), 81.6 (C-CHeCH3).

Ring-opening product of a non-isolated hydantoin has also been isolated (see Scheme S6)


Sodium tert-butoxide, released during the formation of the non-isolated hydantoins, could explain the formation of the dipeptide 29 via a ring-opening reaction.

2-(bis-(2-tert-Butoxycarbonyl)amino-acetylamino)-2-methyl-propionic acid 29 (C16H28N2O7, 360.40 g.mol⁻¹): Hydantoin ring-opening product 29 was obtained when bis-Boc cyclo[−Gly−Aib] was reacted according to the general procedure for the synthesis of hydantoins. The crude reaction mixture was purified using method A (0% to 75% B in 24 min.) yielding compounds 29 with a 12% yield as a colourless oil.

1H NMR (CDCl3, 600 MHz) δ 1.35 (s, 6H, H3C(CH3)); 1.41 (s, 18H, H3C(CH3)); 4.07 (s, 2H, H3C(CH3)); 8.09 (s, 1H, H3C(CH3)); 13C NMR (CDCl3, 150 MHz) δ 24.9 (C-CHeCH3), 27.5 (C-CHeCH3), 47.6 (C-CHeCH3), 54.8 (C-CHeCH3), 81.6 (C-CHeCH3).
(C\(_6\)H\(_3\)N\(_2\)O\(_7\)), 151.6 (C\(_6\)O\(_{\text{Boc}}\)), 166.9 (C\(_6\)O\(_{\text{amide}}\)), 175.3 (C\(_6\)O\(_2\)H); HPLC \(r_t = 1.73\) min; ESI-MS\(^+\) \(m/z\) 383.2 [M+Na]\(^+\); HRMS (TOF ES MS\(^+\)) \(m/z\) calculated for [C\(_{16}\)H\(_{28}\)N\(_2\)O\(_7\) + Na]\(^+\) 383.1794 g mol\(^{-1}\), found 383.1799 g mol\(^{-1}\).

3.5.13 Valine-Phenylalanine derivatives

2-(4-Isopropyl-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-propionic acid 30 (C\(_{15}\)H\(_{18}\)N\(_2\)O\(_4\), 290.31 g mol\(^{-1}\)): Deprotected hydantoin 30 was obtained when bis-Boc cyclo-[Phe-Val] was reacted according to the general procedure for the synthesis of hydantoins. The crude reaction mixture was purified using method B (isochratic elution with 35% B during 20 min.) yielding compounds 30 with a 5% yield as a colourless oil.

\(^1\)H NMR (CD\(_3\)C\(_6\)H\(_2\), 600 MHz) \(\delta\) 1.06 (d, 3H, \(J = 6.9\) Hz, H CH\((\text{CH}_3)_2\)), 1.11 (d, 3H, \(J = 6.9\) Hz, H CH\((\text{CH}_3)_2\)), 1.19 (s, 9H, H CH\((\text{CH}_3)_3\)), 2.28 (dsept, 1H, \(J = 4.9\) Hz, \(J = 14.2\) Hz, HC\((\text{CH}_3)_2\)), 3.31 (dd, 1H, \(J = 9.9\) Hz, \(J = 14.2\) Hz, HC\((\text{CH}_2)\text{Ph}\)), 3.44 (dd, 1H, \(J = 4.5\) Hz, \(J = 14.2\) Hz, HC\((\text{CH}_2)\text{Ph}\)), 4.19 (dd, 1H, \(J = 4.9\) Hz, \(J = 6.2\) Hz, HNC\((\text{CH}_3)\)), 4.97 (dd, 1H, \(J = 4.5\) Hz, \(J = 9.9\) Hz, H COC\((\text{CH}_2)\)), 7.16-7.28 (m, 5H, HA\(_r\)), 8.85 (s, 1H, H N); \(^{13}\)C NMR (CD\(_3\)C\(_6\)H\(_2\), 150 MHz) \(\delta\) 18.4 (CCH\((\text{CH}_3)_2\)), 19.6 (CCH\((\text{CH}_3)_2\)), 27.6 (CCH\((\text{CH}_3)_3\)), 29.4 (CCH\((\text{CH}_2)\text{Ph}\)), 35.8 (CCH\((\text{CH}_2)\)), 59.7 (2C, CNH C\((\text{CH}_2)\)), 84.4 (C(CH\(_3\)), 126.6-138.6 (C\(_A\)), 153.9 (C\(_{\text{COBoc}}\)), 176.9 (C\(_{\text{COBoc}}\)), 178.7 (C\(_{\text{CH(CHOH)}}\)), HPLC \(r_t = 2.18\) min; Chiral HPLC \(r_t = 14.10\) min; ESI-MS\(^+\) \(m/z\) nd; HRMS (TOF ES MS\(^+\)) \(m/z\) calculated for [C\(_{15}\)H\(_{18}\)N\(_2\)O\(_4\) + Na]\(^+\) 313.1164 g mol\(^{-1}\), found 313.1165 g mol\(^{-1}\); \([\alpha]_D^{20} = -60.0\) (C = 0.10, MeOH).

Ring-opening product of a non-isolated hydantoin has also been isolated (see Scheme S7)

Scheme S7. Formation of hydantoin ring-opening products 31+32.

Two diastereoisomers 31 and 32 resulting from the ring opening of the non-isolated hydantoin were purified and characterized. Since we have no clue regarding the stereochemistry, no unknown stereogenic centres was attributed.

2-[3-(1-Carboxy-2-phenyl-ethyl)-3-(tert-Butoxycarbonyl)-ureido]-3-methyl-butyric acid 31 (C\(_{20}\)H\(_{28}\)N\(_2\)O\(_7\), 408.45 g mol\(^{-1}\)): Hydantoin ring-opening product 31 was obtained along deprotected hydantoin 30 with a 14% yield after purification as a colourless oil.

\(^1\)H NMR (CD\(_3\)C\(_6\)H\(_2\), 400 MHz) \(\delta\) 1.06 (d, 3H, \(J = 6.9\) Hz, H\(_{\text{CH(CHOH)}}\)), 1.11 (d, 3H, \(J = 6.9\) Hz, H\(_{\text{CH(CHOH)}}\)), 1.19 (s, 9H, H\(_{\text{CH(CHOH)}}\)), 2.28 (dsept, 1H, \(J = 4.9\) Hz, \(J = 14.2\) Hz, H\(_{\text{CH(CHOH)}}\)), 3.31 (dd, 1H, \(J = 9.9\) Hz, \(J = 14.2\) Hz, H\(_{\text{NHCO}}\)), 3.44 (dd, 1H, \(J = 4.5\) Hz, \(J = 14.2\) Hz, H\(_{\text{CH(CHOH)}}\)), 4.19 (dd, 1H, \(J = 4.9\) Hz, \(J = 6.2\) Hz, H\(_{\text{NHCO}}\)), 4.97 (dd, 1H, \(J = 4.5\) Hz, \(J = 9.9\) Hz, H\(_{\text{COCH(CHOH)}}\)), 7.16-7.21 (m, 5H, HA\(_r\)), 8.85 (s, 1H, H\(_{\text{NH}}\)); \(^{13}\)C NMR (CD\(_3\)C\(_6\)H\(_2\), 100 MHz) \(\delta\) 18.4 (C\(_{\text{CH(CHOH)}}\)), 19.6 (C\(_{\text{CH(CHOH)}}\)), 27.6 (C\(_{\text{CH(CHOH)}}\)), 29.4 (C\(_{\text{CH(CHOH)}}\)), 35.8 (C\(_{\text{CH(CHOH)}}\)), 59.7 (2C, C\(_{\text{NHCO}}\) + C\(_{\text{COCH(CHOH)}}\)), 84.8 (C\(_{\text{CH(CHOH)}}\)).
for \([\text{C}_{20}\text{H}_{28}\text{N}_{2}\text{O}_{7} + \text{Na}^+]\) 431.1794 gmol\(^{-1}\), found 431.1797 gmol\(^{-1}\); HPLC \(t_r = 2.18\) min; Chiral HPLC \(t_r = 15.06\) min; ESI-MS\(^+\) \(m/z\) 431.2 [M+Na]\(^+\); HRMS (TOF ES MS\(^+\)) \(m/z\) calculated for \([\text{C}_{20}\text{H}_{28}\text{N}_{2}\text{O}_{7} + \text{Na}^+]\) 431.1794 gmol\(^{-1}\), found 431.1797 gmol\(^{-1}\); \(\delta_{\text{D}} = -68.7\) (C = 1.10, MeOH).

2-[3-(1-Carboxy-2-phenyl-ethyl)-3-(tert-Butoxycarbonyl)-ureido]-3-methylbutyric acid 32 (C\(_{20}\)H\(_{23}\)N\(_2\)O\(_5\), 408.45 g mol\(^{-1}\)): Hydantoin ring-opening product 32 was obtained along deprotected hydantoin 30 with a 12% yield after purification as a colourless oil.

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.86 (d, 3H, \(J = 6.5\) Hz, H\(_{\text{CH\(_3\)}}\)), 0.87 (d, 3H, \(J = 6.5\) Hz, H\(_{\text{CH\(_3\)}}\)), 1.44 (s, 9H, H\(_{\text{C(CH\(_3\)}}\)), 2.17 (dsept, 1H, \(J = 5.0\) Hz, \(J = 6.5\) Hz, H\(_{\text{CH\(_3\)}}\)), 3.17 (dd, 1H, \(J = 10.2\) Hz, \(J = 14.4\) Hz, H\(_{\text{CH\(_3\)}}\)), 3.40 (dd, 1H, \(J = 5.2\) Hz, \(J = 14.2\) Hz, H\(_{\text{CH\(_3\)}}\)), 4.21 (dd, 1H, \(J = 5.0\) Hz, \(J = 7.3\) Hz, H\(_{\text{NH\(_2\)}}\)), 5.61 (m, 1H, H\(_{\text{C(OH)}}\)), 7.15-7.24 (m, 5H, H\(_{\text{Ar}}\)), 8.94 (s, 1H, H\(_{\text{NH}}\)); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 17.7 (C\(_{\text{CH\(_3\)}}\)), 19.3 (C\(_{\text{CH\(_3\)}}\)), 28.0 (C\(_{\text{C(CH\(_3\)}}\)), 30.3 (C\(_{\text{C(CH\(_3\)}}\)), 35.9 (C\(_{\text{O\(_2\)}}\)), 56.8 (C\(_{\text{NH\(_2\)}}\)), 59.1 (C\(_{\text{CO\(_2\)}}\)), 85.3 (C\(_{\text{CH\(_3\)}}\)), 126.7-137.4 (C\(_{\text{Ar}}\)), 153.8 (C\(_{\text{O\(_2\)}}\)), 154.7 (C\(_{\text{ON\(_2\)}}\)), 167.3 (C\(_{\text{NH\(_2\)}}\)), 177.1 (C\(_{\text{NH\(_2\)}}\)); HPLC \(t_r = 2.18\) min; Chiral HPLC \(t_r = 16.11\) min; ESI-MS\(^+\) \(m/z\) 431.2 [M+Na]\(^+\); HRMS (TOF ES MS\(^+\)) \(m/z\) calculated for \([\text{C}_{20}\text{H}_{23}\text{N}_{2}\text{O}_{5} + \text{Na}^+]\) 431.1794 gmol\(^{-1}\), found 431.1793 gmol\(^{-1}\); \(\delta_{\text{D}} = +100.0\) (C = 0.30, MeOH).

3.5.14 \(\alpha\)-Methyl-Valine (\(\alpha\)-Me-Val) derivatives

(S)-2-(2-((tert-butoxycarbonyl)amino)acetamido)-2,3-dimethylbutanoic acid 33 (C\(_{13}\)H\(_{24}\)N\(_2\)O\(_5\), 288.34 g mol\(^{-1}\)): Hydantoin ring-opening product 33 was obtained when Boc cyclo-[Gly-\(\alpha\)-Me-Val] was reacted according to the general procedure for the synthesis of hydantoins. The crude reaction mixture was purified using method B (0% to 64% B in 16 min.) yielding compounds 33 with a 30% yield as a colourless oil.

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 0.93 (d, 3H, \(J = 6.7\) Hz, H\(_{\text{CH\(_3\)}}\)), 0.96 (d, 3H, \(J = 6.7\) Hz, H\(_{\text{CH\(_3\)}}\)), 1.43 (s, 9H, H\(_{\text{C(CH\(_3\)}}\)), 1.46 (s, 3H, H\(_{\text{C(CH\(_3\)}}\)), 2.33 (m, 1H, H\(_{\text{CH\(_3\)}}\)), 3.70 (dd, 1H, \(J = 16.5\) Hz, \(J = 6.0\) Hz, H\(_{\text{CH\(_3\)}}\)), 3.85 (dd, 1H, \(J = 16.7\) Hz, \(J = 5.7\) Hz, H\(_{\text{CH\(_3\)}}\)), 4.12 (brs, 1H, H\(_{\text{NH\(_2\)}}\)), 6.98 (brs, 1H, H\(_{\text{NH\(_2\)}}\)); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 17.1 (C\(_{\text{CH\(_3\)}}\)), 17.4 (C\(_{\text{CH\(_3\)}}\)), 18.2 (C\(_{\text{CH\(_3\)}}\)), 28.5 (C\(_{\text{CH\(_3\)}}\)), 33.7 (C\(_{\text{CH\(_3\)}}\)), 45.1 (C\(_{\text{NH\(_2\)}}\)), 64.0 (C\(_{\text{C\(_3\)}}\)), 81.0 (C\(_{\text{C\(_3\)}}\)), 156.8 (C\(_{\text{CO\(_2\)}}\)), 171.2 (C\(_{\text{CON\(_2\)}}\)), 175.5 (C\(_{\text{CO\(_2\)}}\)); HPLC \(t_r = 1.46\) min; Chiral HPLC \(t_r = 11.97\) min; ESI-MS\(^+\) \(m/z\) 311.2 [M+Na]\(^+\); HRMS (TOF ES MS\(^+\)) \(m/z\) calculated for [C\(_{13}\)H\(_{24}\)N\(_2\)O\(_5\) + Na\(^-\)] 311.1583 gmol\(^{-1}\), found 311.1578 gmol\(^{-1}\); \(\delta_{\text{D}} = +5.0\) (C = 1.00, MeOH).
4 NMR Spectra
5 References