Supporting Information

**Self-trapped Vibrational States in Synthetic β-sheet helices**

Erik Schwartz, Pavol Bodis, Matthieu Koepf, Jeroen J. L. M. Cornelissen, Alan E. Rowan, Sander Woutersen, and Roeland J. M. Nolte

Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands. E-mails: r.nolte@science.ru.nl, j.cornelissen@science.ru.nl, a.rowan@science.ru.nl

Van ’t Hoff Institute for Molecular Sciences, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands. E-mail: s.woutersen@uva.nl
Epimerisation
To further confirm that it is indeed the C$_1$ that is prone to epimerisation an isocyanide, derived from β-homoalanine instead of alanine was synthesised (see below, scheme S4) and obtained enantiomerically pure, as concluded from the absence of double signals in both the $^1$H NMR and $^{13}$C NMR spectrum. The polymerisation behaviour of this polymer, however, deviated (almost inert to polymerisation) from most other isocyanodipeptides preluding the use of this monomer as a good non-H-bonding model. In contrast to the polymerisation of the β-homoalanine derived isocyanide, polymerisation of 3 proceeded much faster and therefore monomer 3 was chosen for the random copolymerization with 4. We tentatively assigned the low yield of the polymerisation of β-homoalanine derived isocyanide to the chelating of the monomer to the nickel centre hampering the polymerisation process.

Random Copolymer
Incorporation of both monomers into the polymer was demonstrated by varying the ratio between the monomers 3 and 4 (15:1, 1:2, 1:0 and 0:1, respectively). Infrared spectroscopy showed different intensities in NH, Amide I and Amide II vibrations and in NMR spectroscopy differences in the integration of the OCH ($^1$H NMR and $^{13}$C NMR) and NH ($^1$H NMR) resonances were observed.

Incorporation of an N-methylated alanine unit in the isocyanopeptide
Conversion of Boc-L-$N$-methyl-Ala-OH into the corresponding L-$N$-methylalanine methyl ester HCl salt and subsequently coupling to Boc-L-ala-OH using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) give 6 (Scheme S1). Removal of the Boc-protecting group of 6 with HCl gave the HCl salt 7 of the $N$-methylated dipeptide. Conversion into the formamide using similar conditions to previous work, i.e., refluxing in ethyl formate in the presence of sodium formate, was unsuccessful, as illustrated by the absence of the formyl proton and the complete disappearance of the methoxy protons in the $^1$H NMR spectrum. Apparently, the $N$-methylated dipeptide had cyclised by attack of the amine on the ester moiety via the Z-amide (Scheme S2). The formation of diketopiperazines is a known problem with $N$-methylated amino acids. It can be prevented by switching to the tert-butyl ester derivative as illustrated by Wenger (for MeLeu-MeVal-OtBu) and McDermott (Ala-MeLeu-OtBu). The deprotection of Cbz-L-Ala-D-MeAla-OtBu (9) with Pd/H$_2$ followed by reaction of the liberated amine in ethyl formate, however, also resulted in the formation of the cyclised compound 8. To avoid the diketopiperazine formation, $N$-formyl-Ala-OH can be coupled to an $N$-methylated alanine, although in this case there is the disadvantage of epimerisation due to an ‘enhanced reactivity’ of the acid group, however, a successful coupling product could not be obtained.
Scheme S1: Reagents and reaction conditions: (i) SOCl₂, MeOH; (ii) Boc-D-alanine, EDC, HOBT, DIPEA, CH₂Cl₂; (iii) EtOAc·HCl, t-BuOH; (iv) HCO₂Et, NaHCO₃, various conditions / 2,4,5-trichlorophenol, DIPEA, CH₂Cl₂; (v) Boc-D-N-methyl-alanine-OtBu, EDC, HOBT, CH₂Cl₂; (v) Pd/H₂, MeOH.

Scheme S2. Cyclisation of the N-methylated dipeptide via the (Z)-amide.
Scheme S3: Reagents and reaction conditions: (i) (R)-(+) lactate methyl ester, EDC, CH₂Cl₂; (ii) EtOAc·HCl / HCO₂Et, NaHCO₃, reflux (iii) diphosgene, N-Methylmorpholine, CH₂Cl₂, –30°C.

Figure S1: ¹H NMR (300 MHz) spectrum of isocyanide 3 in CDCl₃. Inset shows the two signals attributed to the methoxy protons.
Figure S2: $^{13}$C NMR (75 MHz) spectrum of isocyanide 3 in CDCl$_3$. Inset shows the doubling of the signals for the C=O and O-CH$_3$ carbons.

Figure S3: HPLC chromatogram of isocyanide 3 showing two retention times with similar intensities. (10µL of a 1mg / 1mL solution in isopropanol / heptane (80:20 v/v). Column: ODH2. Detector: 213 nm.)
Scheme S4: Reagents and reaction conditions: (i) Boc-D-Ala-OH, EDC, CH₂Cl₂; (ii) EtOAc·HCl/ HCO₂Et, NaHCO₃, reflux (iii) diphosgene, N-Methylmorpholine, CH₂Cl₂, –30°C. (iv) 0.03 equivalents Ni(ClO₄)₂·6H₂O, MeOH, CH₂Cl₂.

Figure S4: Circular Dichroism spectrum of Polymer 13 in CHCl₃ (13µM).
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009

**General** All solvents were distilled prior to use. All other chemicals were commercials products and used as received. Column chromatography was performed using silica gel (40–60 μm) purchased from Merck. TLC-analyses were carried out on silica 60 F_{254} coated glass from Merck and the compounds were visualised using Ninhydrine, KMnO₄ or Ni(ClO₄)₂·6H₂O in EtOH. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC-300 MHz instrument operating at 300 MHz and 75 MHz respectively, unless otherwise stated. FT-infrared spectra were recorded on a ThermoMattson IR300 spectrometer equipped with a Harrick ATR unit; compounds were measured as solid or oil. Mass spectrometry measurements were performed on a JEOL Accutof instrument (ESI). Optical rotations were measured on a Perkin Elmer 241 Polarimeter at room temperature and are reported in 10⁻¹ deg cm² g⁻¹. LD-PIAA (1)¹, DL-PIAA (4)² were synthesised according to literature procedures. The polymers have typical MWs of 10⁶ g /mol as analysed by AFM.¹, ³ High Performance Liquid Chromatography (HPLC) analysis was performed on a Shimadzu VP LC10 equipped with a 250 mm · 4 · 4.6 mm² Daicel Chiralpak OD-H column, using isocratic flow rates of 1 mL min⁻¹ of hexane and 2-propanol as eluent in various ratios. Detection took place at λ = 215 and 254 nm.

Femto-second pump-probe experiments were carried out using a setup described previously.⁴ Mid-infrared pump and probe pulses with energies of 10 µJ and ~100 nJ respectively, that are independently tunable from 2800 to 4000 cm⁻¹ were generated. The pulses have a duration and bandwidth of 150 fs and ~80 cm⁻¹, respectively. The cross correlation function was measured using two-photon absorption in InAs placed in a sample cell identical to the one used in the experiments on the solution samples. Transient absorption changes were measured as a function of frequency and pump-probe delay time using frequency-dispersed detection of the probe and reference pulses using a 2 × 32 MCT array, and a continuously variable path-length differences between the pump and probe pulses. To cover the entire frequency region of interest, the center frequency of the probe pulse was subsequently tuned to three of four values, chosen such that the observed transient-absorption spectra have sufficient overlap, and the spectra are merged afterwards. The probe polarization was at 45º with respect to that of the pump, and using a polarizer after the sample, either the parallel or the perpendicular polarization component of the probe pulse was measured. All experiments were carried out at room temperature on ~10mM solutions (concentration of repeating unit; to ensure that the results are not dependent on inter-molecular aggregation IR experiments were performed at various concentrations (including more diluted solutions), which did not reveal any changes in
the shift of the NH and amide I vibrational stretches) in CDCl$_3$ kept between two CaF$_2$
windows separated by a 1 mm teflon spacer.

### Compounds

**($S$)-($R$)-1-Methoxy-1-oxopropan-2-yl)2-formamidopropanoate**

The Boc-protecting group of the ‘dipeptide’ (2.12 g, 7.7 mmol) was removed by dissolving
the ‘dipeptide’ in HCl-saturated ethyl acetate (150 mL). The mixture was stirred for 5 hrs
after which time the solvent was evaporated *in vacuo* and the excess of HCl was removed by
addition of $t$-BuOH/CH$_2$Cl$_2$ and subsequent evaporation. The resulting HCl salt was taken up
in ethyl formate (150 mL) and sodium formate (2.15 g, 31.6 mmol, 4.1 equiv) was added. The
mixture was stirred under reflux for 72 hrs, before the solid was filtered off and washed
thoroughly with CHCl$_3$. The salt was removed from the filtrate and the crude product was
purified by column chromatography (2% MeOH in CHCl$_3$) to yield 75% of a colorless oil.
$[\alpha]_D^\text{+} + 17^\circ$ (c 1.2, CHCl$_3$). $^1$H NMR ($\delta$ ppm, CDCl$_3$, 300 MHz): 8.18 (s, 1H, HCO), 6.28 (br,
1H, NH), 5.14 (q, $J = 7.0$ Hz, 1H, OCH), 4.77 (qn, $J = 7.0$ Hz, 1H, NHCH$_2$), 3.74 (s, 3H,
OCH$_3$), 1.51 (d, $J = 7.0$ Hz, 3H, NHCH$_2$CH$_3$), 1.47 (d, $J = 7.0$ Hz, 3H, OCH$_2$CH$_3$). $^{13}$C NMR ($\delta$
ppm, CDCl$_3$, 75 MHz): 171.9, 170.6 (C=O), 160.5 (HCO), 69.7 (OCH), 52.6 (OCH$_3$), 47.0
(NHCH), 18.5 (NHCH$_2$CH$_3$), 17.0 (OCH$_2$CH$_3$). FT-IR (cm$^{-1}$, ATR): 3313 (NH), 1748 (ester),
1683 (Amide I), 1558 (amide II). MS-ESI: m/z = 226 [M+Na]$^+$. HRMS for C$_8$H$_{13}$NO$_5$Na:

**($R$)-($S$)-1-Methoxy-1-oxopropan-2-yl)2-formamidopropanoate**

Following the same procedure as for the ($S,R$) diastereoisomer, the title compound was
obtained in 81% yield as a colorless oil. $[\alpha]_D^\text{+} -17^\circ$ (c 1.2, CHCl$_3$). $^1$H NMR ($\delta$ ppm, CDCl$_3$,
300 MHz): 8.17 (s, 1H, HCO), 5.13 (d, $J = 6.9$ Hz, 1H, NH), 5.12 (q, $J = 7.2$ Hz, 1H, OCH),
4.70 (qn, $J = 7.2$ Hz, 1H, NHCH), 3.75 (s, 3H, OCH$_3$), 1.51 (d, $J = 6.9$ Hz, 3H, NHCHCH$_3$),
1.46 (d, $J = 7.2$ Hz, 3H, OCH$_2$CH$_3$). $^{13}$C NMR ($\delta$ ppm, CDCl$_3$, 75 MHz): 171.3, 170.2 (C=O),
160.9 (HCO), 68.9 (OCH), 51.9 (OCH$_3$), 46.2 (NHCH), 17.2 (NHCH$_2$CH$_3$), 16.2 (OCH$_2$CH$_3$).
FT-IR (cm$^{-1}$, ATR): 3313 (NH), 1746 (ester), 1683 (Amide I), 1558 (amide II). MS-ESI: m/z

**($R$)-1-Methoxy-1-oxopropan-2-yl)2-isocyanopropanoate**

The formamide (305 mg, 1.5 mmol) was dissolved in dry CH$_2$Cl$_2$ (60 mL) under an N$_2$
atmosphere and N-methyl morpholine (0.33 mL, 3.0 mmol, 2.0 equiv) was added. The
resulting solution was cooled to –50 °C (acetone/CO₂) and diphosgene (90 µL, 0.75 mmol, 0.5 equiv) in CH₂Cl₂ (10 mL) was added dropwise to over a period of 30 minutes, while the temperature was maintained at –50 °C. After complete addition of diphosgene, the pale yellow solution was allowed to warm to 0 °C and an ice-cold saturated aqueous sodium bicarbonate solution (3 mL) was added while stirring for 10 minutes. The product was extracted with CHCl₃ (10 mL) and subsequently washed with an aqueous 10% (w/w) sodium bicarbonate solution and water (10 mL). The organic layer was dried (Na₂SO₄) and evaporated in vacuo resulting in a pale yellow oil. The product was purified using column chromatography (2% MeOH in CHCl₃). Analysis by NMR spectroscopy and HPLC revealed epimerisation of the isocyanide. Bulb–to–bulb distillation of the pale yellow isocyanide with a Kugelrohr apparatus offered the epimerised isocyanide 3 as a colorless oil in 60% yield. ¹H NMR (δ ppm, CDCl₃, 300 MHz): 5.12 (m, 2H, OCH), 4.38 (q, J = 7.0 Hz, 2H, NCH), 3.72 (s, 3H, OCH₃), 3.71 (s, 3H, OCH₃), 1.66 (d, J = 7.0 Hz, 3H, NCHCH₃), 1.50 (d, J = 7.0 Hz, 3H, OCHCH₃), 1.49 (d, J = 7.0 Hz, 3H, OCHCH₃). ¹³C NMR (δ ppm, CDCl₃, 75 MHz): 170.1, 170.0 (C=O), 166.7, 166.6 (C=O), 159.9, 159.8 (CN), 70.2, 70.1 (OCH), 52.6, 52.5 (OCH₃), 51.6, 51.5 (NCH), 19.3, 19.3 (NCHCH₃), 16.6, 16.5 (OCHCH₃). FT-IR (cm⁻¹, ATR): 2145 (CN), 1746 (ester). MS-ESI: m/z = 208 [M+Na]⁺. HRMS for C₈H₁₁NO₄Na: Calcd 208.0586. Found: 208.0587. HPLC (Column ODH2, 1 mg/mL, 2-propanol / heptane 4:1 v/v): 7.32 min., 8.29 min.

(5S)-(R)-1-methoxy-1-oxopropan-2-yl)3-formamidobutanoate)

Following the same procedure as for the formamide precursor of 3, the title compound was obtained in 84% yield as a colorless oil. [α]D – 44° (c 1.0, CHCl₃). ¹H NMR (δ ppm, CDCl₃, 200 MHz, rotamers): 7.93 and 7.88 (rotameric s, 1H, HCO), 6.95 and 6.80 (rotameric d, J = 7.3 Hz, 1H, NH₂), 4.90 (q, J = 7.1 Hz, 1H, OCH), 4.24 (sextet, 1H, CH β-homo-Ala), 3.55 (s, 3H, OCH₃), 2.42 (d, J = 5.6 Hz, 2H, CH₂), 1.29 (d, J = 7.1 Hz, 3H, OCHCH₃), 1.11 and 1.06 (rotameric d, J = 6.8 Hz, 3H, CH₃ β-homo-Ala). ¹³C NMR (δ ppm, CDCl₃, 50 MHz, rotamers): 171.0, 170.9, 170.2, 169.8 (rotameric C=O), 164.1, 160.7 (rotameric HCO), 68.5, 68.3 (rotameric OCH), 52.1 (OCH₃), 45.1, 41.4 (rotameric CH β-homo-Ala), 40.6, 39.6 (rotameric CH₂), 21.4, 20.6 (rotameric CH₃ Ala β-homo-Ala), 19.5, 16.5 (rotameric OCHCH₃). FT-IR (cm⁻¹, ATR): 3378 (NH), 1736 (ester), 1661 (Amide I), 1528 (amide II). MS-ESI: m/z = 240 [M+Na]⁺. HRMS for C₉H₁₅NO₆Na: Calcd 240.0848. Found: 240.0858.
(S)-(R)-1-Methoxy-1-oxopropan-2-yl)3-isocyanobutanoate) (β-alanine derived isocyanide)

Following a similar procedure as for 3, 5 was obtained in 68% yield as a colorless oil. [α]D + 68° (c 1.2, CHCl3). 1H NMR (δ ppm, CDCl3, 300 MHz): 5.13 (q, J = 6.9 Hz, 1H, OCH), 4.10 (sextet, J = 6.9 Hz, 1H, CH β-homo-Ala), 3.73 (s, 3H, OCH3), 2.80 (m, 1H, CH2), 2.64 (m, 1H, CH2), 1.49 (d, J = 7.2 Hz, 3H, OCH3), 1.45 (m, 3H, CH2 β-homo-Ala). 13C NMR (δ ppm, CDCl3, 75 MHz): 170.8, 168.8 (C=O), 156.3 (tr, J = 4.6 Hz), 69.2 (OCH), 52.5 (OCH3), 46.4 (tr, J = 6.3 Hz, CH β-homo-Ala), 41.3 (CH2), 21.4, 16.9 (OCH2CH3). FT-IR (cm–1, ATR): 2148 (CN), 1745 (ester). MS-ESI: m/z = 222 [M+Na]+. HRMS for C9H13NO4Na: Calcd 220.0742. Found: 220.0750.

Randomcopolymer 2

To 3 (396 mg, 2.14 mmol) and 4 (26.4 mg, 0.14 mmol, 0.065 equiv) in CH2Cl2 (5mL) was added 0.03 equiv of Ni(ClO4)2·6H2O (90 µL of a 0.85 mM MeOH solution). The solution turned red/brown immediately and after 12 hrs the solvent was evaporated off. The glassy solid was taken up in a minimal amount of THF and the polymer precipitated out by dropping this solution into diethyl ether (200 mL) with vigorous stirring. The product was filtered off and washed extensively with ether. Drying in vacuo gave the polymer as a brown solid in 40% yield. 1H NMR (δ ppm, CDCl3, 300 MHz): 5.3–4.8 (br, 1H, OCH), 4.4–3.9 (br, 2H, NCH, CH ala), 3.9–3.4 (br, 6H, OCH3), 1.9–0.9 (br, 12H, CH3). 13C NMR (δ ppm, CDCl3, 75 MHz): 171 (br, C=O), 70 (br, OCH), 53–53 (br, OCH3, CH), 17.5–16 (br, CH3. FT-IR (cm–1, ATR): 1739 (C=O ester), 1629 (C=N), 1092 (C-O-C).

(S)-Methyl 2-methyl–((R)-2-(tertbutoxycarbonylamino)-N-methylpropanamido)propanoate 6

SOCl2 (6 mL) was slowly added to MeOH (50 mL) at –78 °C. After addition of Boc-L-N-methyl-Ala-OH (2.05 g, 10.1 mmol) the mixture was warmed up to room temperature and stirred for 24 hrs. After this time the reaction mixture was concentrated and t-BuOH/EtOH/CH2Cl2 was added and evaporated under reduced pressure twice, to remove excess HCl. The resulting L-N-methylalanine methyl ester HCl salt was dissolved in CH2Cl2 (200 mL). To this solution Boc-D-alanine-OH (2.19 g, 11.6 mmol, 1.15 equiv), DIPEA (4.0 mL, 23.4 mmol, 2.3 equiv), HOBt (1.74 g, 11.4 mmol, 1.13 equiv) and EDC (2.12 g, 11.0 mmol, 1.09 equiv) were added. After stirring for 18 hrs the reaction mixture was washed with an aqueous 10% (w/w) citric acid solution (2 × 150 mL), H2O (150 mL), aqueous 10 % (w/w)
sodium carbonate solution (2 × 150 mL) and H2O (150 mL). The organic layer was dried (Na2SO4), concentrated and subjected to column chromatography (3% MeOH in CHCl3), yielding 6 in 82% yield as a colorless oil. [α]D – 44° (c 1.1, CHCl3). 1H NMR (δ ppm, CDCl3, 300 MHz, rotamers): 5.51 and 5.39 (br d, J = 7.3 Hz, 1H, NH), 5.03 (q, J = 7.0 Hz, 1H, NHCH), 4.24 (rotameric m, 1H, CH3NCH), 3.75 and 3.70 (rotameric s, 3H, OCH3), 3.00 and 2.82 (rotameric s, 3H, NCH3), 1.47 and 1.40 (rotameric d, J = 7.0 Hz, 3H, CH3NCHCH3), 1.43 (s, 9H, C(CH3)3), 1.30 (d, J = 7.0 Hz, 3H, NHCHCH3). 13C NMR (δ ppm, CDCl3, 75 MHz, rotamers): 173.2, 172.8, 171.8, 171.3 (rotameric C=O), 155.0 (C=O Boc), 79.4 (C(CH3)3), 54.9 and 53.1 (CH3N), 52.6 and 52.3 (rotameric OCH3), 46.6 and 46.1 (rotameric NHCH), 31.8 and 29.3 (rotameric CH2NCH), 28.4 (C(CH3)3), 19.2 and 19.0 (rotameric NHCHCH3), 15.4 and 14.8 (rotameric CH3NCHCH3). FT-IR (cm⁻¹, ATR): 3417, 3314 (NH), 1742 (ester), 1705, 1690 (Amide I), 1645 (N-CH3) 1558 (amide II). MS-ESI: m/z = 311 [M+Na]+. HRMS for C13H24N2O5Na: Calcd 311.1583. Found: 311.1572.

(R)-tert-Butyl 2-((S)-2-(benzyloxy carbonylamino)-N-methylpropanamido)propanoate 9

Starting from Z-L-alanine-OH and D-N-methylalanine tert-butyl ester and following the same procedure as for 6, 9 was obtained in 69 % yield as a colorless oil. [α]D + 41° (c 1.1, CHCl3). 1H NMR (δ ppm, CDCl3, 300 MHz, rotamers): 7.32–7.28 (m, ArH, 5H), 5.85(d, J = 7.5 Hz, 1H, NH), 5.06 (s, 2H, CH2), 4.84 and 4.52 (rotameric q, J = 7.2 Hz, 1H, CH3NCH), 4.65 (rotameric m, 1H, NHCH), 2.97 and 2.80 (rotameric s, 3H, NCH3), 1.43–1.30 (rotameric m, 6H, CH2NCHCH3 and NHCHCH3 ), 1.40 (s, 9H, C(CH3)3). 13C NMR (δ ppm, CDCl3, 75 MHz, rotamers): 172.5, 172.4, 170.3, 169.7 (rotameric C=O), 155.6, 155.5 (rotameric C=O tert-butyl ester), 136.5, 136.4 (rotameric ArC ipso to OCH2), 128.5–127.9 (rotameric m, ArC), 82.4, 81.6 (rotameric C(CH3)3), 66.7, 66.6 (rotameric CH2) 55.7, 54.0 (CH3NCH), 47.1 and 46.8 (rotameric NHCH), 31.9 and 29.1 (rotameric CH3NCH), 27.9, 27.94 (rotameric C(CH3)3), 19.2 and 18.9 (rotameric NHCHCH3), 15.5 and 14.3 (rotameric CH2NCHCH3). FT-IR (cm⁻¹, ATR): 3291 (NH), 1735 (ester), 1716, 1696 (Amide I), 1645 (N-CH3), 1558 (amide II). MS-ESI: m/z = 387 [M+Na]+. HRMS for C19H28N2O5Na: Calcd 311.1583. Found: 311.1572.

(3R, 6S)-1,3,6-Trimethylpiperazine-2,5-dione (cyclo-alanyl-N-alanyl) 8

The title compound was obtained after treatment of 6 or 9 using the reaction conditions described in the text above.
Yield 60 %. Mp: 111 °C. $^1$H NMR (δ ppm, CDCl$_3$, 300 MHz): 7.7 (br, 1H, NH), 4.03 (q, $J$ = 6.9 Hz, 1H, CH), 3.85 (q, $J$ = 7.2 Hz, 1H, CH), 2.93 (s, NCH$_3$3H$\_3$), 1.46 (d, $J$ = 6.9 Hz, 3H, CH$_3$), 1.45 (d, $J$ = 7.2 Hz, 3H, CH$_3$). $^{13}$C NMR (δ ppm, CDCl$_3$, 75 MHz): 172.0, 167.1 (C=O), 58.8, 49.7 (CH), 32.4 (NCH$_3$), 18.3, 17.1 (CH$_3$). FT-IR (cm$^{-1}$, ATR): 3235 (NH), 1648 (br, Amide I).

**((S)-(R)-1-Methoxy-1-oxopropan-2-yl)2-(tert-butoxycarbonylamino)propanoate 10a**

Methyl (R)-(+) lacatate methyl ester (3.1 mL, 32.4 mmol) and Boc-L-alanine-OH (6.86 g, 36.3, 1.1 equiv mmol) were dissolved in CH$_2$Cl$_2$ (200 mL). To this solution diisopropylethylamine (DIPEA; 6.1 mL, 35.7 mmol, 1.1 equiv), 1-hydroxybenztriazole (HOBt; 5.55 g, 36.2 mmol, 1.1 equiv), a catalytic amount of dimethylaminopyridine (DMAP) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 6.83 mmol, 1.1 equiv) were added. After stirring for 10 hrs the solvent was evaporated in vacuo and the product was redissolved in CHCl$_3$ (200 mL). This solution was subsequently washed with an aqueous 10% (w/w) citric acid solution (2 × 200 mL), H$_2$O (200 mL), an aqueous 10% (w/w) sodium carbonate solution (2 × 200 mL) and H$_2$O (200 mL). The organic layer was dried (Na$_2$SO$_4$), concentrated and subjected to column chromatography (2% MeOH in CHCl$_3$), yielding 73% of 10a as a colorless oil.

$[\alpha]$_D + 16° (c 2.1, CHCl$_3$). $^1$H NMR (δ ppm, CDCl$_3$, 300 MHz): 5.13 (q, $J$ = 6.9 Hz, 1H, OCH), 5.06 (br, 1H, NH), 4.34 (m, 1H, NHCH), 3.70 (s, 3H, OCH$_3$), 1.46 (d, $J$ = 6.9 Hz, 3H, OCHCH$_3$), 1.40 (s, 9H, C(CH$_3$)$_3$), 1.38 (d, $J$ = 7.2 Hz, 3H, NHCHCH$_3$). $^{13}$C NMR (δ ppm, CDCl$_3$, 75 MHz): 172.6, 170.8, 155.0 (C=O), 79.8 (C(CH$_3$)$_3$), 69.2 (OCH), 52.4 (OCH$_3$), 49.4 (NHCH), 28.4 (C(CH$_3$)$_3$), 18.5 (NHCHCH$_3$), 16.9 (OCHCH$_3$). FT-IR (cm$^{-1}$, ATR): 3378 (NH), 1745 (ester), 1699 (Amide I), 1510 (amide II). MS-ESI: m/z = 294 [M+Na]$^+$. HRMS for C$_{12}$H$_{21}$NO$_6$Na: Calcd 294.1267. Found: 294.1258.

**(R)-(S)-1-methoxy-1-oxopropan-2-yl)2-(tert-butoxycarbonylamino)propanoate 10b**

Following the same procedure as for 10a, 10b was obtained in 68% yield as a colorless oil.

$[\alpha]$_D –15° (c 0.9, CHCl$_3$). $^1$H NMR (δ ppm, CDCl$_3$, 300 MHz): 5.13 (q, $J$ = 7.0 Hz , 1H, OCH), 5.04 (br, 1H, NH), 4.36 (m, 1H, NHCH), 3.73 (s, 3H, OCH$_3$), 1.49 (d, $J$ = 7.0 Hz, 3H, OCHCH$_3$), 1.43 (s, 9H, C(CH$_3$)$_3$), 1.40 (d, $J$ =7.7 Hz, 3H, NHCHCH$_3$). $^{13}$C NMR (δ ppm, CDCl$_3$, 75 MHz): 172.6, 170.8, 155.1 (C=O), 79.9 (C(CH$_3$)$_3$), 69.3 (OCH), 52.5 (OCH$_3$), 49.4 (NHCH), 28.4 (C(CH$_3$)$_3$), 18.6 (NHCHCH$_3$), 16.9 (OCHCH$_3$). FT-IR (cm$^{-1}$, ATR): 3382
(NH), 1744 (ester), 1711 (Amide I), 1512 (amide II). MS-ESI: m/z = 294 [M+Na]+. HRMS for C_{12}H_{21}NO_{6}Na: Calcd 294.1267. Found: 294.1256.

(R)-(S)-1-methoxy-1-oxopropan-2-yl)2-formamidopropanoate) 11b
Following the same procedure as for the diastereoisomer (S,R), 11b was obtained in 81% yield as a colorless oil. [α]D –17° (c 1.2, CHCl3). 1H NMR (δ ppm, CDCl3, 300 MHz): 8.17 (s, 1H, HCO), 5.13 (d, J = 6.9 Hz, 1H, NH), 5.12 (q, J = 7.2 Hz, 1H, OCH), 4.70 (qn, J = 7.2 Hz, 1H, NHCH), 3.75 (s, 3H, OCH3), 1.51 (d, J = 6.9 Hz, 3H, NHCHCH3), 1.46 (d, J =7.2 Hz, 3H, OCHCH3). 13C NMR (δ ppm, CDCl3, 75 MHz): 171.3, 170.2 (C=O), 160.9 (HCO), 68.9 (OCH), 51.9 (OCH3), 46.2 (NHCH), 17.2 (NHCHCH3), 16.2 (OCHCH3). FT-IR (cm⁻¹, ATR): 3313 (NH), 1746 (ester), 1558 (amide II). MS-ESI: m/z = 226 [M+Na]+. HRMS for C_{8}H_{13}NO_{5}Na: Calcd 226.0691. Found: 226.0694.

(S)-(R)-1-methoxy-1-oxopropan-2-yl)3-(tert-butoxycarbonylamino)butanoate
Starting from Boc-L-ß-homoalanine-OH and Methyl (R)-(+) lactate methyl ester and following the same procedure as for 10a, the title compound was obtained in 76 % yield as a colorless oil. [α]D –14° (c 0.8, CHCl3). 1H NMR (δ ppm, CDCl3, 300 MHz): 5.05 (m, 2H, NH, OCH), 3.69 (s, 3H, OCH3), 2.52 (d, J = 5.4 Hz, 2H, CH₂), 1.42 (d, J = 7.2 Hz, 3H, OCHCH₃), 1.37 (s, 9H, C(CH₃)₃), 1.16 (d, J = 6.6 Hz, 3H, CH₃ ß-homo-Ala). 13C NMR (δ ppm, CDCl3, 75 MHz): 171.2, 170.8, 155.1 (C=O), 79.1 (C(CH₃)₃), 69.3 (OCH), 52.4 (OCH₃), 49.4 (CH β-homo-Ala), 40.3 (CH₂), 28.4 (C(CH₃)₃), 20.1 (CH₃ ß-homo-Ala), 16.9 (OCHCH₃). FT-IR (cm⁻¹, ATR): 3382 (NH), 1740 (ester), 1711, 1688 (Amide I), 1558 (amide II). MS-ESI: m/z = 312 [M+Na]+. HRMS for C_{13}H_{23}NO_{6}Na: Calcd 312.1423. Found: 312.1425.
References


6. Reaction of 2 using various conditions (0-4 equivalent sodium formate, different temperatures, reaction with 2,4,5 trichloro phenyl formate, acetic anhydride / formic acid) give either the cyclised product or no product.

