Supplementary Material (ESI) for Chemical Communications

Supporting Information

Self-trapped Vibrational States in Synthetic β-sheet helices

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Epimerisation

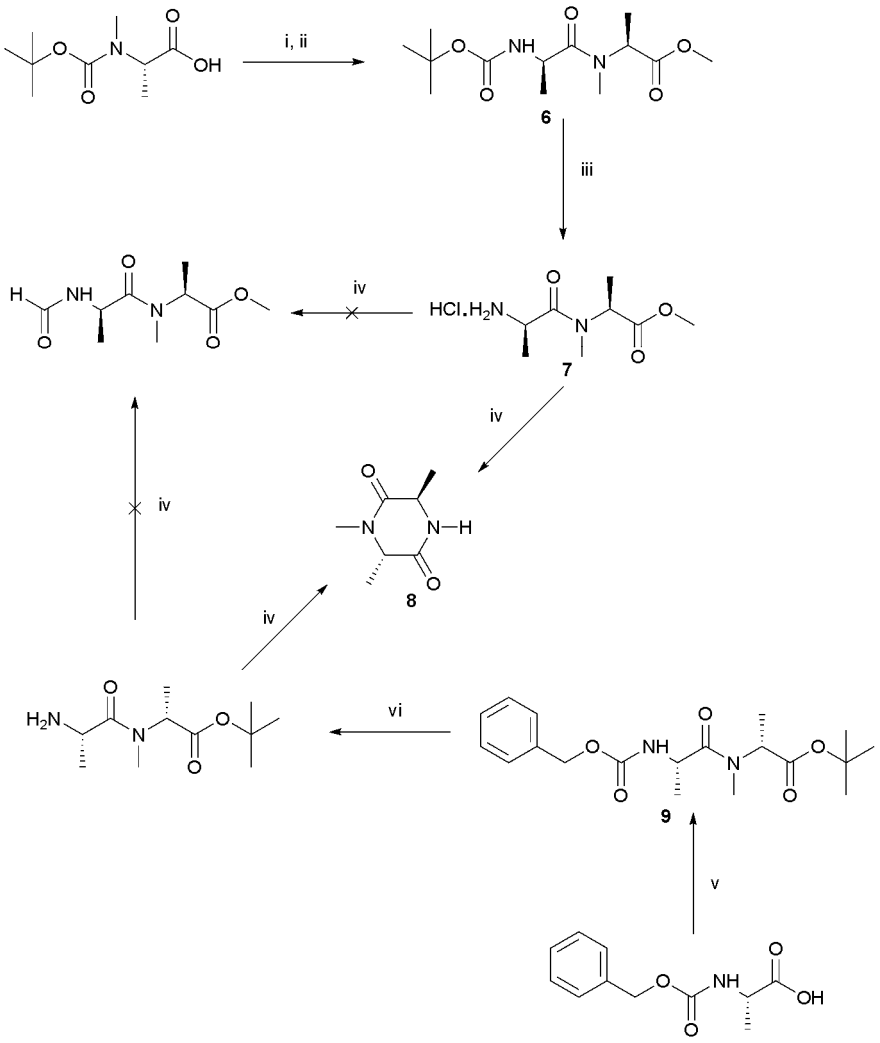
To further confirm that it is indeed the C_1 that is prone to epimerisation an isocyanide, derived from ß-homoalanine instead of alanine was synthesised (see below, scheme S4) and obtained enantiomerically pure, as concluded from the absence of double signals in both the ^{1}H NMR and ^{13}C NMR spectrum. 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 ß-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 ß-homoalanine derived isocyanide to the chelating of the monomer to the nickel centre hampering the polymerisation process.

Random Copolymer

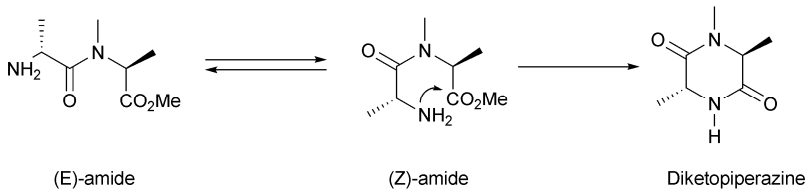
Incorporation of both monomers into the polymer was demonstrated by varying the ratio between the monomers **3** and **4** (15:1, 1:2, 1:0 and 0:1, respectively). Infrared spectroscopy showed different intensities in NH, Amide I and Amide II vibrations and in NMR spectroscopy differences in the integration 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

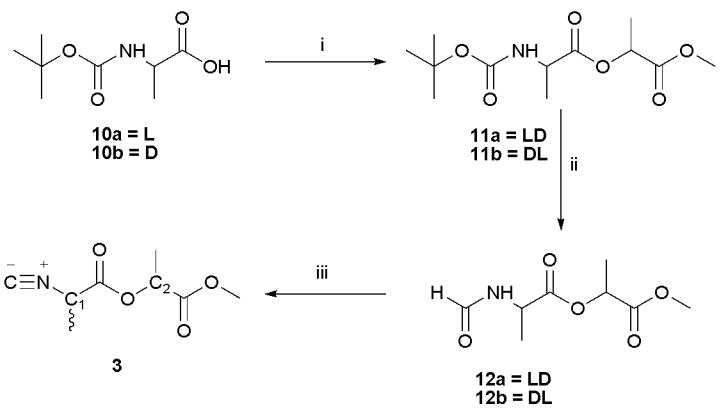
Conversion of Boc-L-*N*-methyl-Ala-OH into the corresponding L-*N*-methylalanine methyl ester HCl salt and subsequently coupling to Boc-L-ala-OH using 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1-hydroxybenzatriazole (HOBt) give **6** (Scheme S1). Removal of the Boc-protecting 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,[5] 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.[6] 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.[7] It can be prevented by switching to the tert-butyl ester derivative as illustrated by Wenger [8] (for MeLeu-MeVal-O^{t}Bu) and McDermott[9] (Ala-MeLeu-O^{t}Bu). The deprotection of *Cbz*-L-Ala-D-MeAla-O^{t}Bu (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) $SOCl_2$, MeOH; (ii) Boc-D-alanine, EDC, HOBt, DIPEA, CH_2Cl_2; (iii) EtOAc·HCl; *t*-BuOH (iv) HCO_2Et, $NaHCO_2$, various conditions / 2,4,5-trichlorophenol, DIPEA, CH_2Cl_2; (v) Boc-D-N-methyl-alanine-O^{t}Bu, EDC, HOBt, CH_2Cl_2; (v) Pd/H_2, MeOH.



Scheme S2. Cyclisation of the *N*-methylated dipeptide via the (Z)-amide.



Scheme S3: Reagents and reaction conditions: (i) (*R*)-(+)-lacatate methyl ester, EDC, CH_2Cl_2; (ii) EtOAc·HCl / HCO_2Et, $NaHCO_2$, reflux (iii) diphosgene, N-Methylmorpholine, CH_2Cl_2, –30ºC.

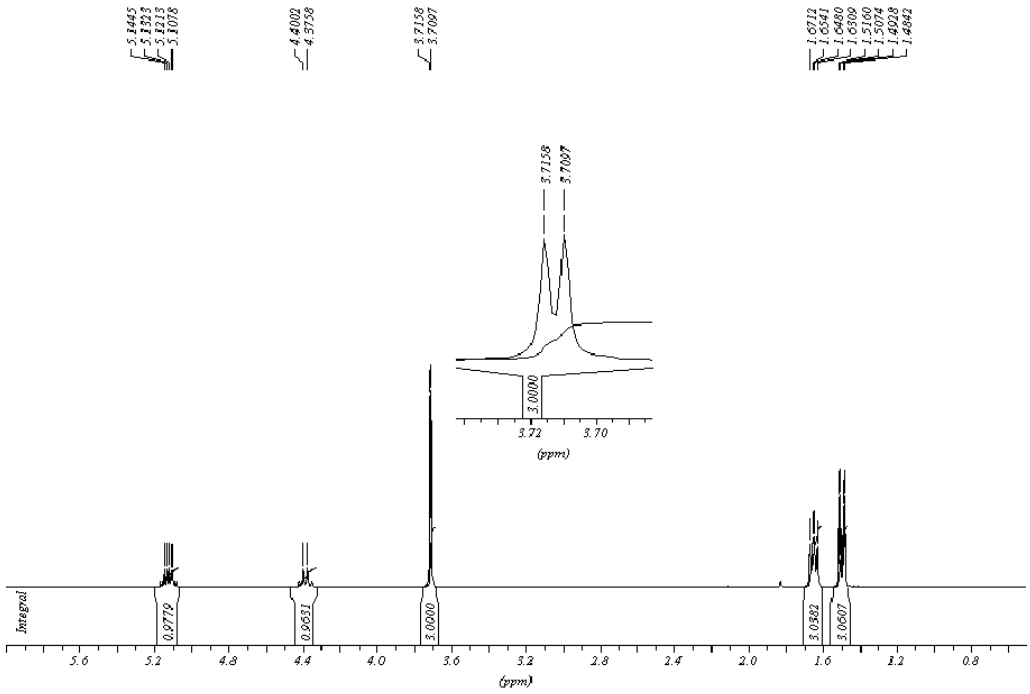


Figure S1: ^{1}H NMR (300 MHz) spectrum of isocyanide 3 in $CDCl_3$. Inset shows the two signals attributed to the methoxy protons.

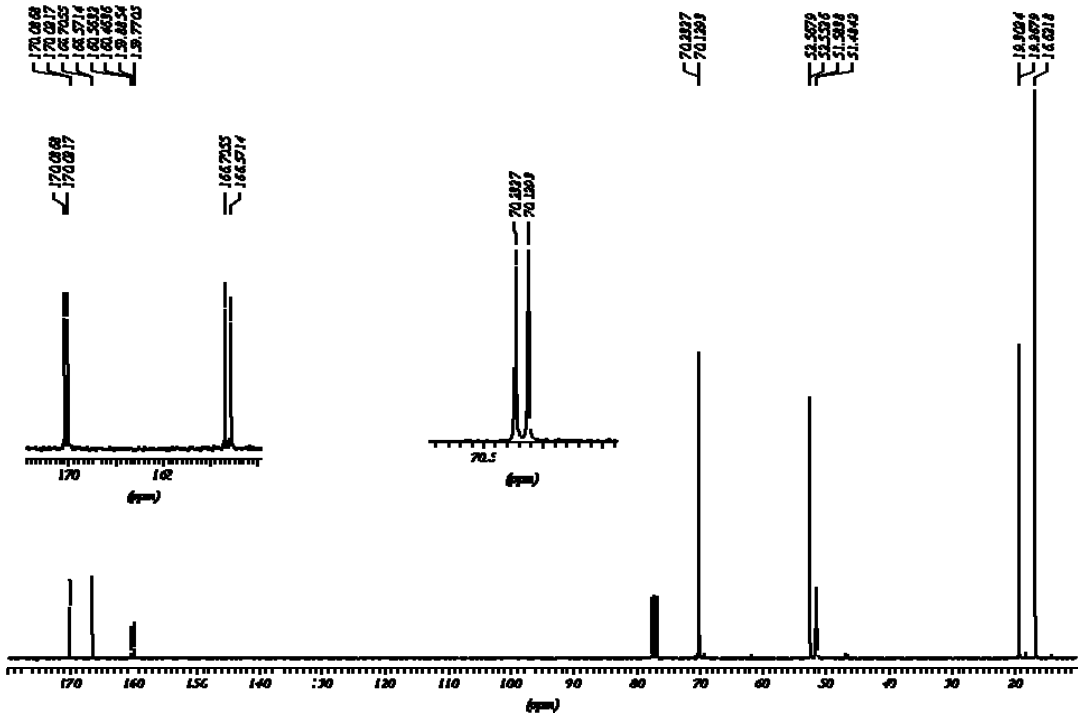


Figure S2: ^{13}C NMR (75 MHz) spectrum of isocyanide 3 in $CDCl_3$. Inset shows the doubling of the signals for the C=O and O-CH_3 carbons.

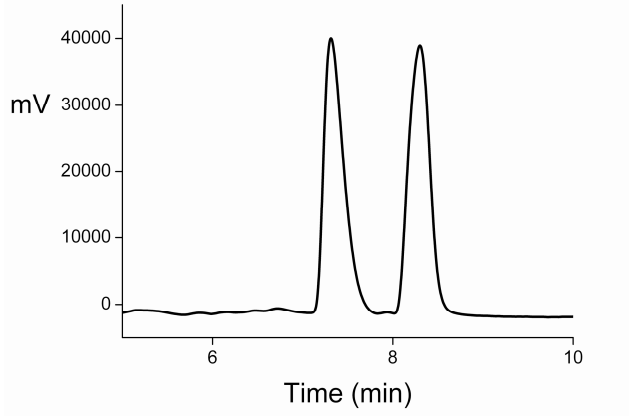
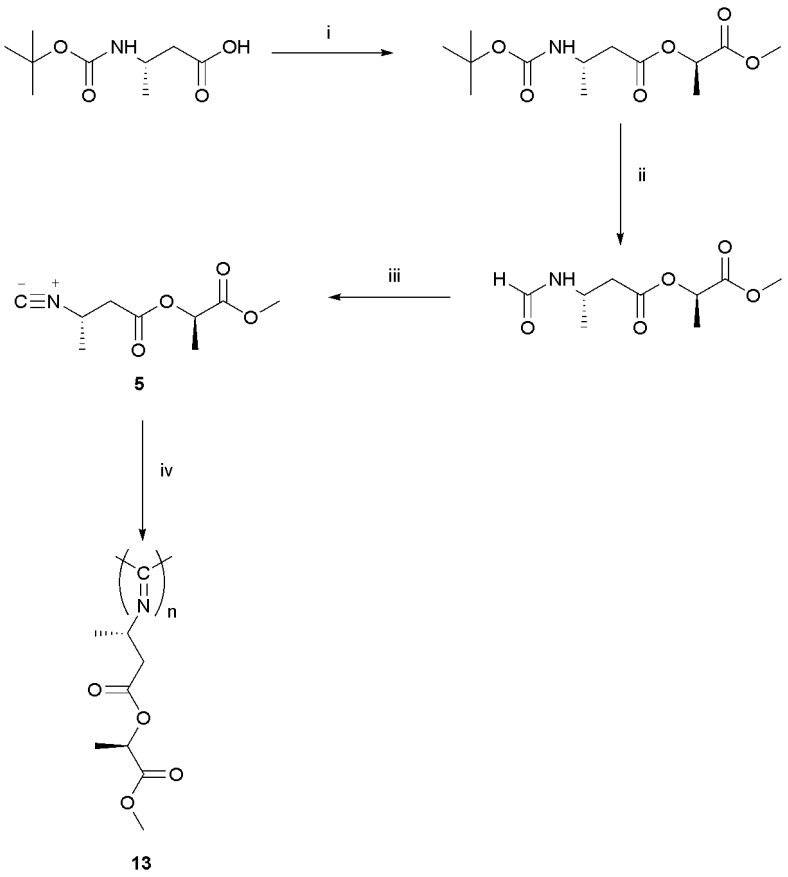


Figure S3: HPLC chromatogram of isocyanide 3 showing two retention times with similar intensities. (10µL of a 1mg / 1mL solution in isopropanol / heptane (80:20 v/v). Column: ODH2. Detector: 213 nm.



Scheme S4: Reagents and reaction conditions: (i) Boc-D-Ala-OH, EDC, CH_2Cl_2; (ii) EtOAc.·HCl/ HCO_2Et, $NaHCO_2$, reflux (iii) diphosgene, N-Methylmorpholine, CH_2Cl_2, –30ºC. (iv) 0.03 equivalents $Ni(ClO_4)_2 \cdot 6H_2O$, MeOH, CH_2Cl_2.

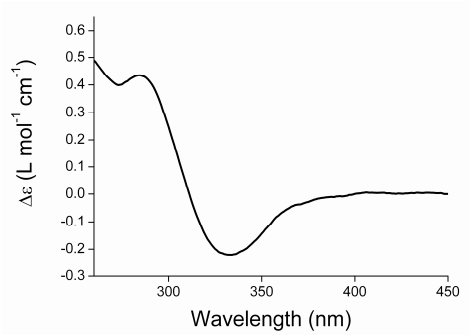


Figure S4: Circular Dichroism spectrum of Polymer **13** in $CHCl_3$ (13μM).

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, $KMnO_4$ or $Ni(ClO_4)_2 \cdot 6H_2O$ in EtOH. ^1H NMR and ^{13}C 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 cm^2 g^{-1}. LD-PIAA (1)[1], DL-PIAA (4)[2] were synthesised according to literature procedures. The polymers have typical MWs of 10^6 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 mm^2 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 $\lambda = 215$ 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_2Cl_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 solvent 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. $[\alpha]_D$ + 17° (*c* 1.2, $CHCl_3$). ^{1}H NMR (δ 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, NHC*H*), 3.74 (s, 3H, OCH_3), 1.51 (d, *J* = 7.0 Hz, 3H, NHCHC*H*$_3$), 1.47 (d, *J* = 7.0 Hz, 3H, OCHC*H*$_3$). ^{13}C NMR (δ 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*C*H$_3$), 17.0 (OCH*C*H$_3$). FT-IR (cm^{-1}, ATR): 3313 (NH), 1748 (ester), 1683 (Amide I), 1558 (amide II). MS-ESI: m/z = 226 $[M+Na]^+$. HRMS for $C_8H_{13}NO_5Na$: Calcd 226.0691. Found: 226.0692.

(*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. $[\alpha]_D$ –17° (*c* 1.2, $CHCl_3$). ^{1}H NMR (δ 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, NHCHC*H*$_3$), 1.46 (d, *J* =7.2 Hz, 3H, OCHC*H*$_3$). ^{13}C NMR (δ 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*C*H$_3$), 16.2 (OCH*C*H$_3$). FT-IR (cm^{-1}, ATR): 3313 (NH), 1746 (ester), 1683 (Amide I), 1558 (amide II). MS-ESI: m/z = 226 $[M+Na]^+$. HRMS for $C_8H_{13}NO_5Na$: Calcd 226.0691. Found: 226.0694.

(*R*)-1-Methoxy-1-oxopropan-2-yl)2-isocyanopropanoate) 3

The formamide (305 mg, 1.5 mmol) was dissolved in dry CH_2Cl_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/CO_2) and diphosgene (90 μL, 0.75 mmol, 0.5 equiv) in CH_2Cl_2 (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 $CHCl_3$ (10 mL) and subsequently washed with an aqueous 10% (w/w) sodium bicarbonate solution and water (10 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* resulting in a pale yellow oil. The product was purified using column chromatography (2% MeOH in $CHCl_3$). 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. ^{1}H NMR (δ ppm, $CDCl_3$, 300 MHz): 5.12 (m, 2H, OCH), 4.38 (q, J = 7.0 Hz, 2H, NCH), 3.72 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 1.66 (d, J = 7.0 Hz, 3H, NCHCH_3), 1.64 (d, J = 7.0 Hz, 3H, NCHCH_3), 1.50 (d, J = 7.0 Hz, 3H, OCHCH_3), 1.49 (d, J = 7.0 Hz, 3H, OCHCH_3). ^{13}C NMR (δ ppm, $CDCl_3$, 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 (OCH_3), 51.6, 51.5 (NCH), 19.3, 19.3 (NCHCH_3), 16.6, 16.5 (OCHCH_3). FT-IR (cm^{-1}, ATR): 2145 (CN), 1746 (ester). MS-ESI: m/z = 208 $[M+Na]^+$. HRMS for $C_8H_{11}NO_4Na$: 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.

(*S*)-((*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. $[\alpha]_D$ – 44° (*c* 1.0, $CHCl_3$). ^{1}H NMR (δ ppm, $CDCl_3$, 200 MHz, rotamers): 7.93 and 7.88 (rotameric s, 1H, HCO), 6.95 and 6.80 (rotameric d, J = 7.3 Hz, 1H, NH,), 4.90 (q, J = 7.1 Hz, 1H, OCH), 4.24 (sextet, 1H, J = 6.5 Hz, CH ß-homo-Ala), 3.55 (s, 3H, OCH_3), 2.42 (d, J = 5.6 Hz, 2H, CH_2,), 1.29 (d, J = 7.1 Hz, 3H, OCHCH_3,), 1.11 and 1.06 (rotameric d, J = 6.8 Hz, 3H, CH_3 ß-homo-Ala). ^{13}C NMR (δ ppm, $CDCl_3$, 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 (OCH_3), 45.1, 41.4 (rotameric CH ß-homo-Ala), 40.6, 39.6 (rotameric CH_2), 21.4, 20.6 (rotameric CH_3 Ala ß-homo-Ala), 19.5, 16.5 (rotameric OCHCH_3). FT-IR (cm^{-1}, ATR): 3378 (NH), 1736 (ester), 1661 (Amide I), 1528 (amide II). MS-ESI: m/z = 240 $[M+Na]^+$. HRMS for $C_9H_{15}NO_6Na$: 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. $[\alpha]_D$ + 68° (*c* 1.2, $CHCl_3$). ^{1}H NMR (δ ppm, $CDCl_3$, 300 MHz): 5.13 (q, *J* = 6.9 Hz, 1H, OCH), 4.10 (sextet, *J* = 6.9 Hz, 1H, CH ß-homo-Ala), 3.73 (s, 3H, OCH_3), 2.80 (m, 1H, CH_2), 2.64 (m, 1H, CH_2), 1.49 (d, *J* = 7.2 Hz, 3H, OCHC*H*$_3$), 1.45 (m, 3H, CH_3 ß-homo-Ala). ^{13}C NMR (δ ppm, $CDCl_3$, 75 MHz): 170.8, 168.8 (C=O), 156.3 (tr, *J* = 4.6 Hz), 69.2 (OCH), 52.5 (OCH_3), 46.4 (tr, *J* = 6.3 Hz, CH ß-homo-Ala), 41.3 (CH_2), 21.4, (CH_3 ß-homo-Ala), 16.9 (OCH*C*H$_3$). FT-IR (cm^{-1}, ATR): 2148 (CN), 1745 (ester). MS-ESI: m/z = 222 $[M+Na]^+$. HRMS for $C_9H_{13}NO_4Na$: 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 CH_2Cl_2 (5mL) was added 0.03 equiv of $Ni(ClO_4)_2 \cdot 6H_2O$ (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. ^{1}H NMR (*δ* ppm, $CDCl_3$, 300 MHz): 5.3–4.8 (br, 1H, OCH), 4.4–3.9 (br, 2H, NCH, CH ala), 3.9–3.4 (br, 6H, OCH_3), 1.9–0.9 (br, 12H, CH_3). ^{13}C NMR (δ ppm, $CDCl_3$, 75 MHz). 171 (br, C=O), 70 (br, OCH), 53–53 (br, OCH_3, CH), 17.5–16 (br, CH_3. 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

$SOCl_2$ (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/CH_2Cl_2 was added and evaporated under reduced pressure twice, to remove excess HCl. The resulting L-*N*-methylalanine methyl ester HCl salt was dissolved in CH_2Cl_2 (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), H_2O (150 mL), aqueous 10 % (w/w)

sodium carbonate solution (2 × 150 mL) and H_2O (150 mL). The organic layer was dried (Na_2SO_4), concentrated and subjected to column chromatography (3% MeOH in $CHCl_3$), yielding 6 in 82% yield as a colorless oil. $[\alpha]_D$ – 44° (*c* 1.1, $CHCl_3$). ^{1}H NMR (δ ppm, $CDCl_3$, 300 MHz, rotamers): 5.51 and 5.39 (br d, *J* = 7.3 Hz, 1H, NH), 5.03 (q, *J* = 7.0 Hz, 1H, NHC*H*), 4.24 (rotameric m, 1H, CH_3NCH), 3.75 and 3.70 (rotameric s, 3H, OCH_3), 3.00 and 2.82 (rotameric s, 3H, NCH_3), 1.47 and 1.40 (rotameric d, *J* = 7.0 Hz, 3H, CH_3NCHCH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.30 (d, *J* = 7.0 Hz, 3H, $NHCHCH_3$). ^{13}C NMR (δ ppm, $CDCl_3$, 75 MHz, rotamers): 173.2, 172.8, 171.8, 171.3 (rotameric C=O), 155.0 (C=O Boc), 79.4 ($C(CH_3)_3$), 54.9 and 53.1 (CH_3NCH), 52.6 and 52.3 (rotameric OCH_3), 46.6 and 46.1 (rotameric NHCH), 31.8 and 29.3 (rotameric CH_3NCH), 28.4 ($C(CH_3)_3$), 19.2 and 19.0 (rotameric $NHCHCH_3$), 15.4 and 14.8 (rotameric CH_3NCHCH_3). FT-IR (cm^{-1}, ATR): 3417, 3314 (NH), 1742 (ester), 1705, 1690 (Amide I), 1645 (N-CH_3) 1558 (amide II). MS-ESI: m/z = 311 $[M+Na]^+$. HRMS for $C_{13}H_{24}N_2O_5Na$: Calcd 311.1583. Found: 311.1572.

(*R*)-*tert*-Butyl 2-((*S*)-2-(benzyloxycarbonylamino)-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.

$[\alpha]_D$ + 41° (*c* 1.1, $CHCl_3$). ^{1}H NMR (δ ppm, $CDCl_3$, 300 MHz, rotamers): 7.32–7.28 (m, ArH, 5H), 5.85(d, *J* = 7.5 Hz, 1H, NH), 5.06 (s, 2H, CH_2), 4.84 and 4.52 (rotameric q, *J* = 7.2 Hz, 1H, CH_3NCH), 4.65 (rotameric m, 1H, NHC*H*), 2.97 and 2.80 (rotameric s, 3H, NCH_3), 1.43–1.30 (rotameric m, 6H, CH_3NCHCH_3 and $NHCHCH_3$), 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (δ ppm, $CDCl_3$, 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 OCH_2), 128.5–127.9 (rotameric m, ArC), 82.4, 81.6 (rotameric $C(CH_3)_3$), 66.7, 66.6 (rotameric CH_2) 55.7, 54.0 (CH_3NCH), 47.1 and 46.8 (rotameric NHCH), 31.9 and 29.1 (rotameric CH_3NCH), 27.9, 27.94 (rotameric $C(CH_3)_3$), 19.2 and 18.9 (rotameric $NHCHCH_3$), 15.5 and 14.3 (rotameric CH_3NCHCH_3). FT-IR (cm^{-1}, ATR): 3291 (NH), 1735 (ester), 1716, 1696 (Amide I), 1645 (N-CH_3), 1558 (amide II). MS-ESI: m/z = 387 $[M+Na]^+$. HRMS for $C_{19}H_{28}N_2O_5Na$: Calcd 387.1896. Found: 387.1889.

(3*R*, 6*S*)-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,), 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_2Cl_2 (200 mL). To this solution diisopropylethylamine (DIPEA; 6.1 mL, 35.7 mmol, 1.1 equiv), 1-hydroxybenzatriazole (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_2O (200 mL), an aqueous 10 % (w/w) sodium carbonate solution (2 × 200 mL) and H_2O (200 mL). The organic layer was dried (Na_2SO_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, OC*H*), 5.06 (br, 1H, NH), 4.34 (m, 1H, NHC*H*), 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 $C_{12}H_{21}NO_6Na$: 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, NHC*H*), 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 $C_{12}H_{21}NO_6Na$: 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. $[\alpha]_D$ –17° (*c* 1.2, $CHCl_3$). ^1H NMR (δ 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, NHCHC*H*$_3$), 1.46 (d, *J* =7.2 Hz, 3H, OCHC*H*$_3$). ^{13}C NMR (δ 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*C*H_3), 16.2 (OCH*C*H_3). FT-IR (cm^{-1}, ATR): 3313 (NH), 1746 (ester), 1683 (Amide I), 1558 (amide II). MS-ESI: m/z = 226 $[M+Na]^+$. HRMS for $C_8H_{13}NO_5Na$: 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*)-(+)-lacatate methyl ester and following the same procedure as for 10a, the title compound was obtained in 76 % yield as a colorless oil. $[\alpha]_D$ –14° (*c* 0.8, $CHCl_3$). ^1H NMR (δ ppm, $CDCl_3$, 300 MHz): 5.05 (m, 2H, NH, OCH), 3.97 (m, 1H, CH ß-homo-Ala), 3.69 (s, 3H, OCH_3), 2.52 (d, *J* = 5.4 Hz, 2H, CH_2), 1.42 (d, *J* = 7.2 Hz, 3H, OCHC*H*$_3$), 1.37 (s, 9H, $C(CH_3)_3$), 1.16 (d, *J* = 6.6 Hz, 3H, CH_3 ß-homo-Ala). ^{13}C NMR (δ ppm, $CDCl_3$, 75 MHz): 171.2, 170.8, 155.1 (C=O), 79.1 (*C*$(CH_3)_3$), 69.3 (OCH), 52.4 (OCH_3), 49.4 (CH ß-homo-Ala), 40.3 (CH_2), 28.4 (C(*C*$H_3)_3$), 20.1 (CH_3 ß-homo-Ala), 16.9 (OCH*C*H_3). FT-IR (cm^{-1}, ATR): 3382 (NH), 1740 (ester), 1711, 1688 (Amide I), 1513 (amide II). MS-ESI: m/z = 312 $[M+Na]^+$. HRMS for $C_{13}H_{23}NO_6Na$: Calcd 312.1423. Found: 312.1425.

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