J Chem Crystallogr (2011) 41:1722–1728
DOI 10.1007/s10870-011-0164-x

ORIGINAL PAPER

Crystal Structures of Dipeptides Derived from the β-Amino Acids (1*R*,2*S*)-2-Aminocyclopentanecarboxylic Acid and (1*S*,2*R*,3*S*)-2-Amino-3-methylcyclopentanecarboxylic Acid

Elin Abraham · Stephen G. Davies · Paul M. Roberts · Amber L. Thompson · James E. Thomson

Received: 28 March 2011 / Accepted: 29 June 2011 / Published online: 19 July 2011

Abstract Crystals of the dimeric β-peptides **13** and **20**, derived from (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid and (1*S*,2*R*,3*S*)-2-amino-3-methylcyclopentanecarboxylic acid, respectively, were synthesised and studied by X-ray diffraction in order to establish their solid state secondary structural characteristics. Compound **13** crystallises in the monoclinic space group P 2_1 with cell parameters of $a = 5.2682(1)$ Å, $b = 9.1211(2)$ Å, $c = 22.4467(6)$ Å, $\beta = 91.3855(9)°$, $V = 1078.29(4)$ Å^3 and $Z = 2$. Compound **20** crystallizes in the orthorhombic space group P 2_1 2_1 2_1 with cell parameters of $a = 5.0968(1)$ Å, $b = 11.5546(2)$ Å, $c = 43.5414(8)$ Å, $V = 2564.22(8)$ Å^3 and $Z = 4$. In both cases adjacent molecules are linked by a series of N–H···O=C hydrogen bonds to form β-sheet like structures.

Keywords β-Peptides · β-Sheet · Asymmetric synthesis · Lithium amide · Parallel kinetic resolution

Introduction

Within the field of peptidomimetics, β-peptides are known to offer improved bioavailability and therapeutic lifetimes when compared to the α-amino acid derived analogues [1–5] whilst still displaying potent biological activity [6–8]; as such they have been the subject of several investigations [9–28]. Within this area we have recently reported studies concerning the secondary structural characteristics of β-peptides derived from (*S*,*S*)-2-aminocyclopentanecarboxylic acid [(*S*,*S*)-ACPC or (*S*,*S*)-transpentacin] [29]. These studies indicated that hexamer **5** and pentamer **4** persist as a 12-helix in both the solid state and solution phase. The conformational traits of a 12-helix were also exhibited by oligomers with as few as three residues in the solid state, although in solution trimer **2** was found to exist as an equilibrium of many alternative conformers whilst tetramer **3** has been shown to predominantly exist in either a 12-helix or turn-type conformation. Furthermore, the introduction of C(3)-alkyl substitution around the 2-aminocyclopentanecarboxylic acid scaffold did not affect the secondary structural preferences and, for example a 12-helical secondary structure was adopted in the solid state and solution phase conformations of C(3)-substituted hexamers **6** and **7** (Fig. 1) [30].

Fülöp et al. [31] have reported that pentamer **8**, derived from (1*R*,2*S*)-ACPC [(1*R*,2*S*)-cispentacin], forms a non-polar strand and adopts a sheet-like structure in solution. We therefore proposed to investigate the effect of introducing C(3)-alkyl substituents around the 2-aminocyclopentanecarboxylic acid scaffold on the secondary structure of this class of β-peptides **9** and report herein our crystallographic studies on both the substituted and unsubstituted dimers ($n = 2$, R = Me or H) (Fig. 2).

Experimental

Boc-[(1*R*,2*S*)-ACPC]$_2$-O^{t}Bu 13

Step 1: A stirred solution of **11** [32] (2.76 g, 14.9 mmol, 97:3 dr, >98% ee) in $CHCl_3$ (25 mL) was successively treated with Et_3N (10.4 mL, 74.5 mmol), HOBt (2.42 g,

E. Abraham · S. G. Davies (✉) · P. M. Roberts · A. L. Thompson · J. E. Thomson
Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK
e-mail: steve.davies@chem.ox.ac.uk

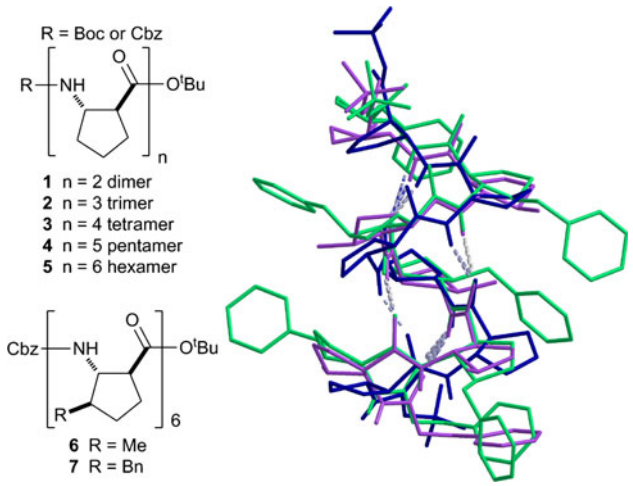


Fig. 1 β-Peptides **1**-**7** and the overlaid X-ray crystal structures of **5** (*blue*, R = Boc), **6** (*purple*) and **7** (*green*) (selected H atoms are omitted for clarity) (Color figure online)

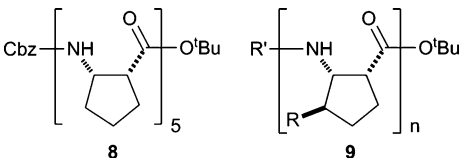


Fig. 2 Pentamer **8** [derived from (1*R*,2*S*)-ACPC] and C(3)-substituted β-peptides **9**

17.9 mmol), **10** [33] (3.92 g, 14.9 mmol, >99:1 dr, >98% ee) and EDC·HCl (3.43 g, 17.9 mmol) under anhydrous conditions. After 16 h, the reaction mixture was washed sequentially with 1.0 M aq HCl (20 mL), satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via recrystallisation ($CHCl_3$/heptane) gave **12** as a white crystalline solid (3.88 g, 61%, >99:1 dr); mp 92–94 °C ($CHCl_3$/heptane); $[\alpha]_D^{18}$ − 64.4 (*c* 1.1 in $CHCl_3$); ν_{max} (KBr) 3335 (N–H), 1717, 1697, 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.47–2.07 (12H, m, 2 × C(3)*H*$_2$, 2 × C(4)*H*$_2$, 2 × C(5)*H*$_2$), 2.69–2.78 (1H, m, C(1)*H*), 2.84 (1H, app q, *J* 7.5, C(1)*H*), 4.11–4.23 (1H, m, C(2)*H*), 4.38–4.48 (1H, m, C(2)*H*), 5.04 (1H, d, *J* 12.5, OC*H*$_A$H$_B$Ph), 5.11 (1H, d, *J* 12.5, OCH$_A$*H*$_B$Ph), 5.43 (1H, d, *J* 7.5 N*H*), 6.20 (1H, d, *J* 8.5 N*H*), 7.28–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.2, 22.7, 28.0, 28.3, 32.4, 32.8 (2 × *C*(3), 2 × *C*(4), 2 × *C*(5)), 28.1 (C*Me*$_3$), 47.3, 48.2 (2 × *C*(1)), 52.0, 54.6 (2 × *C*(2)), 66.2 (O*C*H$_2$Ph), 80.8 (*C*Me$_3$), 128.0, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 136.5 (*i*-*Ph*), 156.1 (N*C*O [carbamate]), 173.0, 173.7 (N*C*O [amide], *C*O$_2^t$Bu); *m*/*z* (ESI$^+$) 453 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}N_2NaO_5^+$ ([M + Na]$^+$) requires 453.2360; found 453.2360.

Step 2: Pd(OH$_2$)/C (25% by wt., 34 mg) was added to a stirred, degassed solution of **12** (134 mg, 0.31 mmol, >99:1 dr) and Boc_2O (75 mg, 0.34 mmol) in MeOH (5 mL). The resulting suspension was stirred under H_2 (1 atm) for 16 h, after which time the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated in vacuo. Purification via recrystallisation ($CHCl_3$/heptane) gave **13** as a white crystalline solid (70 mg, 57%, >99:1 dr); mp 149–150 °C ($CHCl_3$/heptane); $[\alpha]_D^{21}$ − 74.2 (*c* 0.6 in $CHCl_3$); ν_{max} (KBr) 3376, 3342 (N–H), 1715, 1687, 1653, 1525 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35–2.05 (12H, m, 2 × C(3)*H*$_2$, 2 × C(4)*H*$_2$, 2 × C(5)*H*$_2$) overlapping 1.42 (9H, s, C*Me*$_3$) and 1.43 (9H, s, C*Me*$_3$), 2.64–2.75 (1H, m, C(1)*H*), 2.82–2.91 (1H, m, C(1)*H*), 4.05–4.17 (1H, m, C(2)*H*), 4.40–4.51 (1H, m, C(2)*H*), 5.12 (1H, d, *J* 7.9, N*H*), 6.19 (1H, d, *J* 8.5, N*H*); δ_C (100 MHz, $CDCl_3$) 22.2, 22.6, 28.0, 28.2, 32.5, 32.7 (2 × *C*(3), 2 × *C*(4), 2 × *C*(5)), 28.1, 28.4 (2 × C*Me*$_3$), 47.3, 47.8 (2 × *C*(1)), 52.0, 54.1 (2 × *C*(2)), 79.0, 80.8 (2 × *C*Me$_3$), 155.6 (N*C*O [carbamate]), 173.2, 173.7 (N*C*O [amide], *C*O$_2^t$Bu); *m*/*z* (ESI$^+$) 419 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{36}N_2NaO_5^+$ ([M + Na]$^+$) requires 419.2516; found 419.2515.

Cbz-[(1*S*,2*R*,3*S*)-3-Me-ACPC]$_2$-O^{t}Bu 20

Step 1: DDQ (8.60 g, 370 mmol) was added to a stirred solution of **15** [34] (8.60 g, 190 mmol, >99:1 dr) in MeCN/water (v/v 5:1, 190 mL). The resultant mixture was stirred at rt for 32 h then satd aq K_2CO_3 (200 mL) was added. The organic layer was washed sequentially with satd aq K_2CO_3 (2 × 100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 2% → 33% EtOAc in 40–60 °C petrol) gave **16** as a colourless oil (2.81 g, 49%, >99:1 dr); $[\alpha]_D^{18}$ + 183 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3331, 2957, 1722, 1455, 1366, 1147, 761, 701; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.1, C(3)*Me*), 0.96–1.08 (1H, m, C(5)*H*$_A$), 1.29 (3H, d, *J* 6.5, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 1.58 (1H, br s, N*H*), 1.67–1.95 (4H, m, C(3)*H*, C(4)*H*$_2$, C(5)*H*$_B$), 2.35–2.44 (1H, m, C(1)*H*), 2.85–2.94 (1H, m, C(2)*H*), 3.91 (1H, q, *J* 6.5, C(α)*H*), 7.81–7.46 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 25.3 (C(α)*Me*), 27.9 (C*Me*$_3$), 28.3 (*C*(5)), 32.4 (*C*(4)), 42.3 (*C*(3)), 53.3 (*C*(1)), 56.2 (*C*(2)), 67.6 (*C*(α)), 79.9 (*C*Me$_3$), 126.9, 126.9, 128.3 (*o*,*m*,*p*-*Ph*), 146.1 (*i*-*Ph*), 176.4 (*C*O$_2^t$Bu); *m*/*z* (ESI$^+$) 304 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_2^+$ ([M + H]$^+$) requires 304.2271; found 304.2276.

Step 2: Pd(OH)$_2$/C (25% by wt., 870 mg) was added to a stirred, degassed solution of **16** (3.48 g, 11.5 mmol, >99:1 dr) in MeOH/AcOH (v/v 40:1, 41 mL). The resulting suspension was stirred under H_2 (5 atm) for 36 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (40 mL) and washed with satd aq $NaHCO_3$ (3 × 40 mL) and brine (40 mL), then dried and

concentrated in vacuo to give **17** as a colourless oil (1.88 g, 82%, >99:1 dr) [34]; $[\alpha]_D^{21}$ − 46.4 (*c* 1.2 in $CHCl_3$); {lit. [34] for enantiomer $[\alpha]_D^{22}$ + 51.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5, C(3)*Me*), 1.08–1.21 (1H, m, C(4)H_A), 1.44 (2H, br s, NH_2), 1.47 (9H, s, CMe_3), 1.72–2.00 (4H, m, C(3)*H*, C(4)H_B, C(5)H_2), 2.80–2.88 (1H, m, C(1)*H*), 2.92 (1H, app t, *J* 7.5, C(2)*H*).

Step 3: Et_3N (1.04 mL, 7.48 mmol) and CbzCl (1.07 mL, 7.48 mol) were added sequentially to a stirred solution of **17** (1.36 g, 6.80 mmol, >99:1 dr) in anhydrous THF (200 mL) at 0 °C. The resultant mixture was then allowed to warm to rt and stirred for 16 h before the addition of brine (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 2% → 18% EtOAc in 40–60 °C petrol) gave **18** as a colourless oil (2.09 g, 92%, >99:1 dr); $[\alpha]_D^{21}$ + 74.2 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3337 (N–H), 1725 (br), 1512 (C=O); δ_H (400 MHz, $CDCl_3$)1.02 (3H, d, *J* 6.3, C(3)*Me*), 1.11–1.27 (1H, m, C(4)H_A), 1.40 (9H, s, CMe_3), 1.80–2.02 (4H, m, C(3)*H*, C(4)H_B, C(5)H_2), 2.96–3.06 (1H, m, C(1)*H*), 3.76 (1H, app q, *J* 9.4, C(2)*H*), 5.10 (2H, s, OCH_2Ph), 5.21 (1H, d, *J* 9.4, N*H*), 7.26-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(3)*Me*), 26.8, 39.7 (*C*(4), *C*(5)), 28.0 (CMe_3), 31.1 (*C*(3)), 46.9 (*C*(1)), 60.2 (*C*(2)), 66.6 (O*C*H_2Ph), 80.7 (*C*Me_3), 128.0, 128.1, 128.5 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 156.2 (N*C*O), 174.2 (*C*O_2^tBu); *m*/*z* (ESI^+) 334 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{28}NO_4^+$ ($[M + H]^+$) requires 334.2013; found 334.2022.

Step 4: TFA (3 mL) was added to a stirred solution of **18** (1.73 g, 5.20 mmol, >99:1 dr) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 3 h before being concentrated in vacuo and dried under high vacuum to give **19** as a colourless oil (1.19 g, 83%, >99:1 dr); $[\alpha]_D^{23}$ + 44.3 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 3290 (br, N–H, O–H), 1714, 1517 (C=O); δ_H (400 MHz, MeOH-d_4) 0.99 (3H, d, *J* 6.5, C(3)*Me*), 1.09–1.24 (1H, m, C(4)H_A), 1.83–2.13 (4H, m, C(3)*H*, C(4)H_B, C(5)H_2), 2.90 (1H, app q, *J* 7.6, C(1)*H*), 3.70 (1H, app t, *J* 7.6, C(2)*H*) 5.02 (1H, d, *J* 12.3, OCH_AH_BPh), 5.12 (1H, d, *J* 12.3, OCH_AH_BPh), 7.26–7.40 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 17.1 (C(3)*Me*), 26.4 (*C*(5)), 31.3 (*C*(4)), 38.8 (*C*(3)), 46.8 (*C*(1)), 61.0 (*C*(2)), 66.4 (O*C*H_2Ph), 127.7, 127.9, 128.4 (*o*,*m*,*p*-*Ph*), 137.4 (*i*-*Ph*), 157.8 (N*C*O), 176.9 (*C*O_2H); *m*/*z* (ESI^-) 276 ($[M - H]^-$, 100%); HRMS (ESI^-) $C_{15}H_{18}NO_4^-$ ($[M–H]^-$) requires 276.1241; found 276.1240.

Single Crystal X-ray Diffraction

Single crystal diffraction data for **13** and **20** were collected using a Nonius κ-CCD diffractometer (Mo-Kα radiation, λ = 0.71073 Å) at 150(2) K with an Oxford Cryosystems Cryostream N_2 open-flow cooling device [35] and processed using the DENZO-SMN package [36], including unit cell parameter refinement and inter-frame scaling (which were carried out using SCALEPACK within DENZO-SMN).

The structures were solved using SIR92 [37]. Refinement was carried out using full-matrix least-squares within the CRYSTALS suite [38], on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms on nitrogen atoms were generally visible in the difference map and their positions and isotropic displacement parameters were refined using restraints prior to inclusion into the model with riding constraints [39]. The Flack *x* parameters [40, 41] for **13** and **20** were determined to be 0.5(17) and −1.4(14), and analysis [42, 43] of the Bijvoet pairs gave Hooft *y* parameters [44] of −0.3(7) and 0.01(5), respectively. The Bayesian analysis gave the probability that the structure of **13** is the correct enantiomer as 77% assuming enantiopurity and 49% allowing for the possibility of racemic twinning; the corresponding values of 82 and 53% were obtained for **20**. In the absence of a significant anomalous signal, the Friedel pairs were merged for the final refinement for both structures.

Selected structural details for **13** and **20** are included in Table 1 and full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 815399 and 815400, respectively. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and Discussion

β-Peptides **13** and **20** were prepared in accordance with our previously optimised coupling procedures [29, 30].[1] Thus, coupling of the monomer acid **10** [33] and monomer amine **11** [34][2] was achieved with HOBt/EDC·HCl to give dimer **12** in >97:3 dr. Purification of the reaction mixture via recrystallisation ($CHCl_3$/heptane) gave dimer **12** in 61%

[1] It was found that 2,6-di-*tert*-butylphenol (2,6-DTBP) was not compatible with preparing large quantities (>10 g) of the prerequisite β-amino ester in the lithium amide conjugate addition step. Thus, an alternative, scalable procedure was developed using 2-pyridone to quench the lithium β-amino enolate which produced a 97:3 mixture of C(2)-epimeric β-amino esters. For other diastereoselective protonations of lithium β-amino enolates with 2-pyridone from our laboratory, see Refs. [45–47].

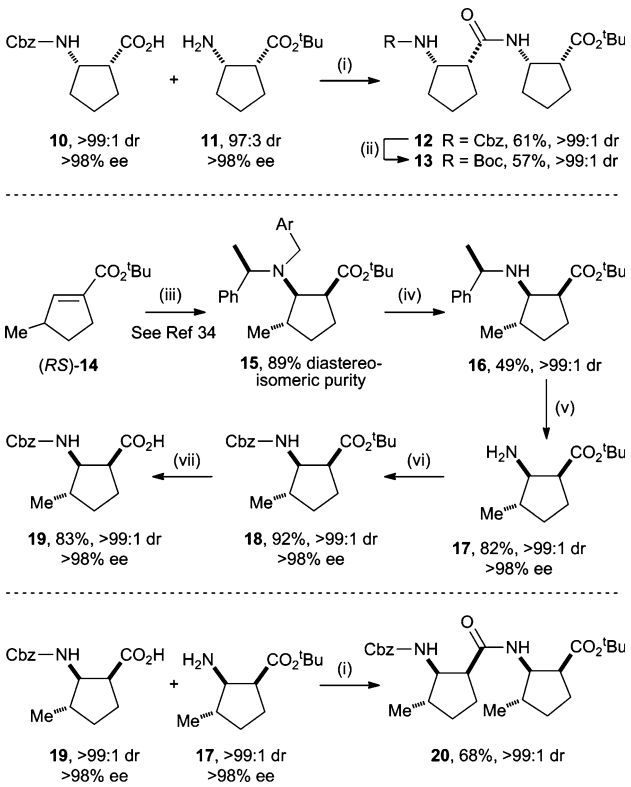
[2] β-Amino ester (1*R*,2*S*)-**11** was converted to the corresponding (*R*)- and (*RS*)-MTPA derivatives (Mosher's amides) and was determined to be >98% ee by both ^{1}H and ^{19}F NMR spectroscopic analyses. See Refs. [48–50].

Table 1 Crystallographic data and refinement details for compounds **13** and **20**

Compound	**13**	**20**
Empirical formula	$C_{21}H_{36}N_2O_5$	$C_{26}H_{38}N_2O_5$
Formula weight	396.53	458.60
Crystal habit, colour	Plate, colourless	Plate, colourless
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a (Å)	5.2682(1)	5.0968(1)
b (Å)	9.1211(2)	11.5546(2)
c (Å)	22.4467(6)	43.5414(8)
α (°)	90	90
β (°)	91.3855(9)	90
γ (°)	90	90
Volume (Å^3)	1078.29(4)	2564.22(8)
Z	2	4
Density (calc. g cm^{-3})	1.221	1.188
Temperature (K)	190	190
Radiation type/λ (Å)	Mo Kα/0.71073	Mo Kα/0.71073
Absorption coeff. (mm^{-1})	0.086	0.082
F(000)	432	992
Crystal size (mm)	0.05 × 0.10 × 0.10	0.20 × 0.30 × 0.30
Reflections measured	4833	5334
Independent reflections	2596	3272
R_{int}	2.5%	2%
Observed reflns. [$I > 2.0\sigma(I)$]	1595	2001
Number of parameters	253	298
Goodness-of-fit on F^2	1.112	1.103
Final R indices [$I > 2.0\sigma(I)$]	$R_1 = 0.038$, $wR_2 = 0.067$	$R_1 = 0.042$, $wR_2 = 0.091$
R indices [all data]	$R_1 = 0.083$, $wR_2 = 0.076$	$R_1 = 0.082$, $wR_2 = 0.103$
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.18, −0.16	0.19, −0.18
CCDC deposition no.	815399	815400

isolated yield as a single diastereoisomer (>99:1 dr). Subsequent treatment of dimer **12** with Boc_2O and $Pd(OH)_2/C$ under an atmosphere of H_2 gave Boc-[(1*R*,2*S*)-ACPC]$_2$-O^{t}Bu **13** in 57% yield and >99:1 dr. Recrystallisation of **13** from $CHCl_3$/heptane gave colourless prisms which were subjected to X-ray diffraction analysis.

The monomeric units **19** and **17** were prepared from (*RS*)-**14** using our previously reported parallel kinetic resolution (PKR) methodology [30, 34, 51, 52]. Oxidative removal of the *N*-(3,4-dimethoxybenzyl) group within **15** was achieved upon treatment with DDQ [34]. Thus, under the optimised conditions for this transformation treatment of β-amino ester **15** (89% diastereoisomeric purity) [34] with DDQ gave **16** in 49% isolated yield and >99:1 dr after



Scheme 1 *Reagents and conditions*: (*i*) EDC·HCl, HOBt, NEt_3, $CHCl_3$, rt, 16 h; (*ii*) $Pd(OH)_2/C$, Boc_2O, H_2 (1 atm), MeOH, rt, 16 h; (*iii*) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (50:50 mixture), THF, −78 °C, 3 h, then NH_4Cl (satd, aq); (*iv*) DDQ, CH_2Cl_2/H_2O (5:1 v/v), rt, 32 h; (*v*) $Pd(OH)_2/C$, H_2 (5 atm), MeOH/AcOH (40:1 v/v), 36 h; (*vi*) CbzCl, NEt_3, THF, 0 °C to rt, 16 h; (*vii*) TFA/CH_2Cl_2 (1:3 v/v), 0 °C to rt, 3 h. [Ar = 3,4-dimethoxyphenyl]

purification via flash column chromatography. Subsequent removal of the *N*-α-methylbenzyl group via hydrogenolysis gave **17** in 82% yield, >99:1 dr and >98% ee.[3] Treatment of **17** with CbzCl gave **18** in 92% yield followed by TFA promoted ester hydrolysis to give *N*-Cbz protected β-amino acid **19** in 83% yield, >99:1 dr and >98% ee. Utilising the HOBt/EDC·HCl/$CHCl_3$ mediated protocol, monomer acid **19** and monomer amine **17** were coupled to give Cbz-[(1*S*,2*R*,3*S*)-3-Me-ACPC]$_2$-O^{t}Bu **20** in 68% yield and >99:1 dr (Scheme 1). Recrystallisation of **20** from CH_2Cl_2/pentane gave colourless prisms which were subjected to X-ray diffraction analysis. Unfortunately, all attempts at the recrystallisation of the corresponding trimers, tetramers and pentamers (which were all prepared using our standard coupling methodology) [29, 30] were unsuccessful.

The molecular structures of **13** and **20** are illustrated in (Fig. 3). In both cases the adjacent molecules are linked by

[3] β-Amino ester (1*S*,2*R*,3*S*)-**17** was converted to the corresponding (*R*)- and (*RS*)-MTPA derivatives (Mosher's amides) and was determined to be >98% ee by both ^{1}H and ^{19}F NMR spectroscopic analyses. See Refs. [48–50].

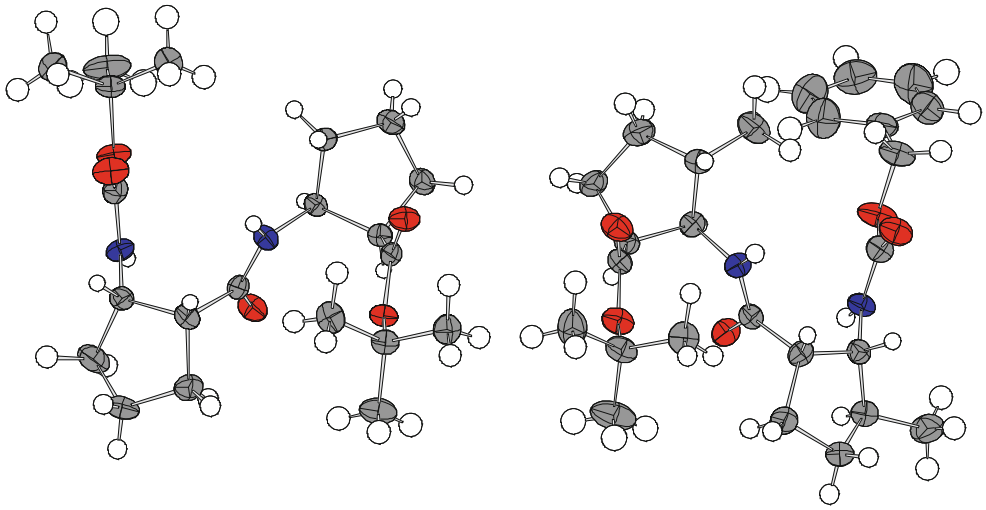


Fig. 3 Molecular structure of **13** (*left*) and **20** (*right*), showing the displacement ellipsoids drawn at the 50% probability level

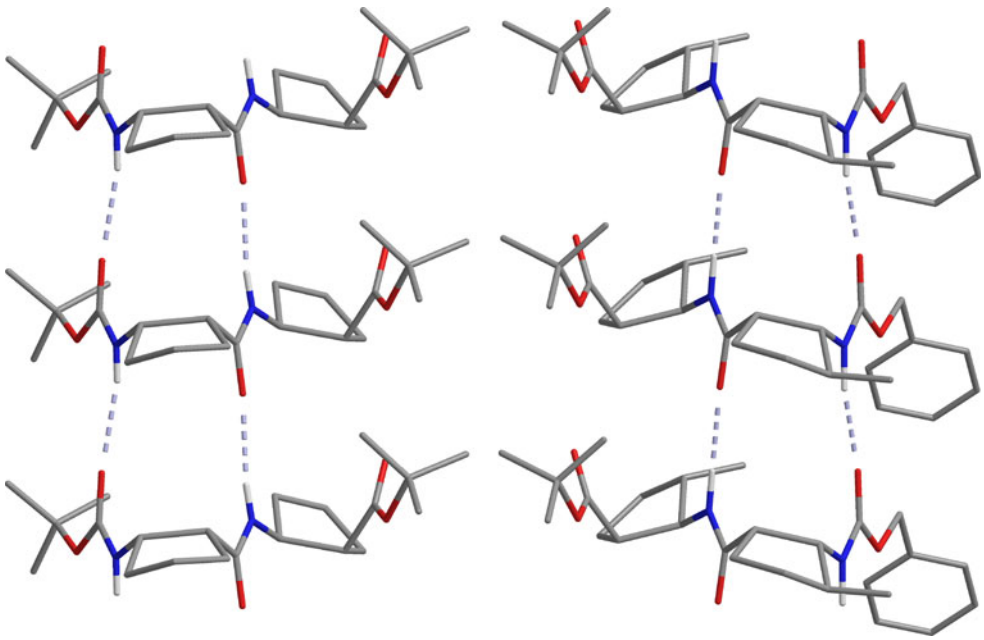


Fig. 4 H-bonding within the crystal structures of **13** (*left*) and **20** (*right*), selected H atoms are omitted for clarity. Hydrogen bonding interactions are shown as a dotted line forming R2,2(14) rings that connect together to give C2,2(14) chains [for **13**: N–H···O=3.141(4), 3.106(4) Å; for **20**: N–H···O=3.062(4), 2.994(4) Å]

a series of intermolecular N–H···O=C hydrogen bonds to form tape-like arrangements in the crystal structure formed from R2,2(14) rings (Fig. 4) [53]. There is excellent parity between the two structures despite them possessing different N-protecting groups and differing by virtue of the additional C(3)-methyl group in each of the monomeric units within **20**. As the two peptides were synthesised in the opposite enantiomeric series (with respect to the parent 2-aminocyclopentanecarboxylic acid scaffold), **20** has been represented as its antipode so that the two structures can be overlaid[4] for comparison (Fig. 5). The C(3)-methyl groups within **20** do not, therefore, disrupt the hydrogen bonding in the solid state. This finding is consistent with our observations that C(3)-methyl substitution does not disrupt the helical secondary structure of β-peptides derived from the epimeric β-amino acid (1*S*,2*S*,3*R*)-2-amino-3-methylcyclopentanecarboxylic acid [30].

Whilst it was not possible to produce crystals of the corresponding trimers, tetramers or pentamers which were suitable for X-ray crystallographic analyses, a combination of IR, ^{1}H NMR and CD spectroscopic analyses confirmed that these oligomers display traits indicative of *intermolecular* hydrogen bonding and are therefore consistent with a similar conformation in solution.

[4] The structures of **13** and *ent*-**20** were overlaid using the Chem-3D structure mapping function.

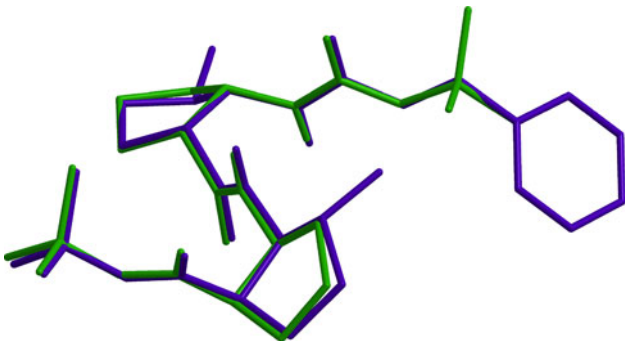


Fig. 5 Overlaid molecular structures of **13** (*green*) and *ent*-**20** (*purple*), selected H atoms are omitted for clarity

Conclusion

In conclusion, the crystal structures of the β-peptides Boc-[(1*R*,2*S*)-ACPC]$_2$-O^{t}Bu **13** and Cbz-[(1*S*,2*R*,3*S*)-3-Me-ACPC]$_2$-O^{t}Bu **20**, derived from (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid and (1*S*,2*R*,3*S*)-2-amino-3-methylcyclopentanecarboxylic acid respectively, were studied by X-ray diffraction. In both cases adjacent molecules are linked by a series of N–H···O=C hydrogen bonds to form sheet like structures.

Supporting Information

Full crystallographic data for **13** and **20** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 815399 and 815400, respectively. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

1. Seebach D, Overhand M, Kuhnle FNM, Martinoni B, Oberer L, Hommel U, Widmer H (1996) Helv Chim Acta 79:913
2. Hintermann T, Seebach D (1997) Chimia 50:244
3. Seebach D, Abele S, Schreiber JV, Martinoni B, Nussbaum AK, Schild H, Schulz H, Hennecke H, Woessner R, Bitsch F (1998) Chimia 52:734
4. Seebach D, Hook DF, Glätti A (2006) Biopolymers (Peptide Science) 84:23
5. Aguilar M-I, Purcell AW, Devi R, Lew R, Rossjohn J, Smith I, Perlmutter P (2007) Org Biomol Chem 5:2884
6. Werder M, Hauser H, Abele S, Seebach D (1999) Helv Chim Acta 82:1774
7. Hamuro Y, Schneider JP, DeGrado WF (1999) J Am Chem Soc 121:12200
8. Liu D, DeGrado WF (2001) J Am Chem Soc 123:7553
9. Hintermann T, Seebach D (1997) Synlett:437
10. Seebach D, Abele S, Gademann K, Guichard G, Hintermann T, Jaun B, Matthews JL, Schreiber JV (1998) Helv Chim Acta 81:932
11. Gung BW, Zou D (1999) J Org Chem 64:2176
12. Raguse L, Lai JR, Gellman SH (2002) Helv Chim Acta 85:4154
13. Glättli A, Seebach D, van Gunsteren WF (2004) Helv Chim Acta 87:24872
14. Luppi G, Galeazzi R, Garavelli M, Formaggio F, Tomasini C (2004) Org Biomol Chem 2:2187
15. Izquierdo S, Kogan MJ, Parella T, Moglioni AG, Branchadell V, Giralt E, Ortuño RM (2004) J Org Chem 69:5093
16. Appella DH, Christianson LA, Karle IL, Powell DR, Gellman SH (1996) J Am Chem Soc 118:13071
17. Barchi JJ Jr, Huang X, Appella DH, Christianson LA, Durell SR, Gellman SH (2000) J Am Chem Soc 122:2711
18. Appella DH, Christianson LA, Klein DA, Powell DR, Huang X, Barchi JJ Jr, Gellman SH (1997) Nature 387:381
19. Applequist J, Bode KA, Appella DH, Christianson LA, Gellman SH (1998) J Am Chem Soc 120:4891
20. Wang X, Espinosa JF, Gellman SH (2000) J Am Chem Soc 122:4821
21. Lee H-S, Syud FA, Wang X, Gellman SH (2001) J Am Chem Soc 123:7721
22. Winkler JD, Piatnitski EL, Mehlmann J, Kasparec J, Axelsen PH (2001) Angew Chem Int Ed 40:743
23. Woll MG, Fisk JD, LePlae PR, Gellman SH (2002) J Am Chem Soc 124:12447
24. Raguse L, Lai JR, Gellman SH (2003) J Am Chem Soc 125:5592
25. Park J-S, Lee H-S, Lai JR, Kim BM, Gellman SH (2003) J Am Chem Soc 125:8539
26. Peelen TJ, Chi Y, English EP, Gellman SH (2004) Org Lett 6:4411
27. Simpson GL, Gordon AH, Lindsay DM, Promsawan N, Crump MP, Mulholland K, Hayter BR, Gallagher T (2006) J Am Chem Soc 128:10638
28. Martinek TA, Mándity IM, Fülöp L, Tóth GK, Vaas E, Hollósi M, Forró E, Fülöp F (2006) J Am Chem Soc 128:13539
29. Abraham E, Bailey CW, Claridge TDW, Davies SG, Ling KB, Odell B, Rees TL, Roberts PM, Russell AJ, Smith AD, Smith LJ, Storr HR, Sweet MJ, Thompson AL, Thomson JE, Tranter GE, Watkin DJ (2010) Tetrahedron: Asymmetry 21:1797
30. Abraham E, Claridge TDW, Davies SG, Odell B, Roberts PM, Russell AJ, Smith AD, Smith LJ, Storr HR, Sweet MJ, Thomson JE, Thompson AL, Tranter GE, Watkin DJ (2011) Tetrahedron: Asymmetry 22:69
31. Martinek TA, Tóth GK, Vaas E, Hollósi M, Fülöp F (2002) Angew Chem Int Ed 41:1718
32. Davies SG, Ichihara O, Lenoir I, Walters IAS (1994) J Chem Soc Perkin Trans 1:1411
33. Davies SG, Russell AJ, Sheppard RL, Smith AD, Thomson JE (2007) Org Biomol Chem 5:3190
34. Davies SG, Garner AC, Long MJC, Smith AD, Sweet MJ, Withey JM (2004) Org Biomol Chem 2:3355
35. Cosier J, Glazer AM (1986) J Appl Crystallogr. 19:105
36. Otwinowski Z, Minor W (1997) Methods Enzymol Academic Press, New York, pp 307–326
37. Altomare A, Cascarano G, Giacovazzo C, Guagliardi A, Burla MC, Polidori G, Camalli M (1994) J Appl Crystallogr 27:435
38. Betteridge PW, Carruthers JR, Cooper GI, Prout CK, Watkin DJ (2003) J Appl Crystallogr 36:1487
39. Cooper RI, Thompson AL, Watkin DJ (2010) J Appl Cryst 43:1100
40. Flack HD (1983) Acta Cryst A 39:876
41. Flack HD, Bernardinelli G (2000) J Appl Cryst 33:1143
42. Thompson AL, Watkin DJ (2009) Tetrahedron: Asymmetry 20:712

43. Thompson AL, Watkin DJ (2011) J Appl Cryst submitted manuscript
44. Hooft RWW, Straver LH, Spek AL (2008) J Appl Cryst 41:96
45. Beddow JE, Davies SG, Smith AD, Russell, AJ (2004) Chem Commun:2778
46. Beddow JE, Davies SG, Ling KB, Roberts PM, Russell AJ, Smith AD, Thomson JE (2007) Org Biomol Chem 5:2812
47. Davies SG, Foster EM, McIntosh CR, Roberts PM, Rosser TE, Smith AD, Thomson JE (2011) Tetrahedron: Asymmetry. doi: 10.1016/j.tetasy.2011.06.008
48. Dale JA, Mosher HS (1973) J Am Chem Soc 95:512
49. Sullivan GR, Dale JA, Mosher HS (1973) J Org Chem 38:2143
50. Ohtani I, Kusumi T, Kashman Y, Kakisawa H (1991) J Am Chem Soc 113:4092
51. Aye Y, Davies SG, Garner AC, Roberts PM, Smith AD, Thomson JE (2008) Org Biomol Chem 6:2195
52. Abraham E, Davies SG, Docherty AJ, Ling KB, Roberts PM, Russell AJ, Thomson JE, Toms SM (2008) Tetrahedron: Asymmetry 19:1356
53. Bernstein J, Davis RE, Shimoni L, Chang N-L (1995) Angew Chem Int Ed 34:1555