Supplementary Material (ESI) for Chemical Communications

Parallel sheet structure in cyclopropane γ-peptides stabilized by C-H···O hydrogen bonds

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1. **General experimental procedures.**
2. **Experimental procedures and data for all compounds.**
3. **Proton and carbon NMR spectra for compounds 1, 9 and 3.**

1. General experimental procedures.

1.1 Solvents and Reagents

THF was distilled under an atmosphere of dry nitrogen from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane; dichloromethane was distilled from calcium hydride; triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Reactions performed under an atmosphere of hydrogen gas were maintained by an inflated balloon. pH 7 Buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 ml). All other reagents and solvents were used as supplied, without prior purification.

1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass plates coated with Merck 60 F_{254} silica and visualization was achieved by UV light or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh).

1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker Avance 700 (^{1}H: 700 MHz), a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) or Bruker Avance Cryo 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz). Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak, and are reported (based on appearance rather than interpretation) as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant J /Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet].

1.4 Infrared Spectroscopy

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer fitted with an attenuated total reflectance attachment with internal referencing.

1.5 Mass Spectrometry

Accurate mass measurements were performed on a Finnigan MAT 900 XLT (ES+) at the EPSRC National Mass Spectrometry Service Centre at Swansea.

1.6 Polarimetry

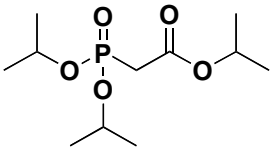
Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm.

1.7 Melting points

Melting points were recorded on a Kofler hot block and are uncorrected.

2. Experimental procedures and data.

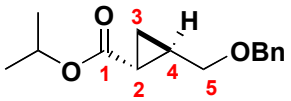
Triisopropylphosphonoacetate



A mixture of triisopropylphosphite (24.0 mL, 185.4 mmol) and isopropyl bromoacetate (58 mL, 234.3 mmol) was stirred at 80°C for 6h. The reaction mixture was distilled under reduced pressure to give triisopropylphosphonoacetate as a colourless oil (37.5 g, 149.4 mmol, 80.6%).

B. p. 88°C/0.4 Torr; ν_{max} /cm^{-1} (film): 1730 (C=O), 1258 (P=O), 1101, 979; δ_H (400 MHz, $CDCl_3$) 5.0 (1H, sept, J 6.3, C*H*$(CH_3)_2$), 4.79-4.68 (2H, m, 2POC*H*$(CH_3)_2$), 2.85 (1H, d, J 21.6, PCH_2), 1.31 (12H, dt, J 6.1, 3.3, 2POCH(CH_3)$_2$), 1.22 (6H, d, J 6.3, OCH(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 165.4 (C), 71.2 (CH), 68.9 (CH), 36.4, 35.0 (PCH_2), 23.9 (CH_3), 21.6 (CH_3).

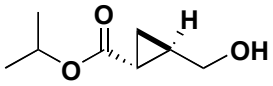
Isopropyl (1*R*, 2*R*)-2-[(benzyloxy)methyl]cyclopropanecarboxylate 5



Triisopropylphosphonoacetate (30.6 g, 121.9 mmol) was added dropwise over 15 mins to a stirring suspension of sodium hydride (5.14 g, 128.5 mmol, 60% in mineral oil) in toluene (130 mL) at 0ºC. Isopropanol (60 µL) was added, and after stirring at room temperature for 10 mins, (*S*)-benzylglycidyl ether **4** (10.00 g, 60.9 mmol) in toluene (30 mL), was added dropwise and the mixture was heated to 60ºC. After 10 h, TLC (EtOAc/petrol, 1:1) indicated complete consumption of starting material (R_f 0.82), to two major products. The reaction mixture was heated at 90ºC for 8 h before being cooled to room temperature, diluted with saturated ammonium chloride (100 mL) and water (200 mL), and extracted with EtOAc (3x200 mL). The collected organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (ether/petrol, 1:4), to yield the cyclopropane **5** (13.9 g, 55.9 mmol, 92%) as a colourless oil.

R_f 0.29 (ether/petrol, 1:4); $[\alpha]_D^{25}$ = 57.9 (32.2 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 2980 and 2865 (CH), 1717 (C=O), 1454, 1180, 1103, 736, 697; δ_H (400 MHz, $CDCl_3$) 7.29-7.18 (5H, m, Ar*H*), 4.91 (1H, sept, J 6.3, C*H*$(CH_3)_2$), 4.45 (2H, s, PhCH_2O), 3.33 (2H, d, J 6.3, H5, H5'), 1.69-1.61 (1H, m, H4), 1.47-1.43 (1H, m, H2), 1.16 (3H, d, J 6.3, OCH(CH_3)(CH_3)), 1.15 (3H, d, J 6.3, OCH(CH_3)(CH_3)), 1.12 (1H, dd, J 8.9, 4.5, H3), 0.77 (1H, ddd, J 8.4, 6.3, 4.3, H3'); δ_C (100 MHz, $CDCl_3$) 173.2 (C), 138.1 (C), 128.4 (CH), 127.6 (CH), 72.6 (CH_2), 71.5 (CH_2), 67.7 (CH), 21.8 (CH(*C*H_3)$_2$), 21.3 (CH), 18.8 (CH), 12.9 (CH_2); *m/z* HRMS (+ESI) found: $[M+Na]^+$ 271.1311; $C_{15}H_{20}O_3Na$ requires 271.1304.

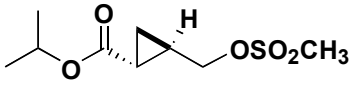
Isopropyl (1*R*, 2*R*)-2-(hydroxymethyl)cyclopropanecarboxylate 5a



A solution of **5** (8.0 g, 32.2 mmol) in ethanol (35 mL) was stirred in the presence of 10% palladium on activated carbon (Degussa type, 10 wt %, 800 mg). The reaction mixture was deoxygenated by three cycles of evacuation and purging with nitrogen before being evacuated, purged with hydrogen gas, and stirred under an atmosphere of hydrogen (maintained by inflated balloon). After 1h, TLC (EtOAc/petrol, 1:1) indicated complete conversion of the starting material (R_f 0.90) to a single product (R_f 0.47). The reaction mixture was filtered through Celite^{TM} and washed with ethanol. Solvents were removed *in vacuo* to yield the alcohol **5a** (5.0 g, 31.6 mmol, 98%), which was used without further purification.

R_f 0.34 (EtOAc/petrol, 1:2); $[\alpha]_D^{25}$ = 64.6 (24.6 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3415 (OH), 2982, 2938 and 2874 (CH), 1719 (C=O), 1454, 1178, 1107; δ_H (400 MHz, $CDCl_3$) 4.98 (1H, sept, J 6.3, C*H*$(CH_3)_2$), 3.59 (1H, dd, J 11.4, 6.1, H5), 3.48 (1H, dd, J 11.4, 6.8, H5'), 1.83 (1H, brs, OH), 1.74-1.66 (1H, m, H4), 1.54-1.49 (1H, m, H2), 1.23 (3H, d, J 6.3, OCH(C*H*$_3$)(CH_3)), 1.22 (3H, d, J 6.3, OCH(CH_3)(C*H*$_3$)), 1.20-1.16 (1H, m, H3'), 0.83 (1H, ddd, J 8.4, 6.3, 4.3, H3); δ_C (100 MHz, $CDCl_3$) 173.2 (C), 67.9 (CH), 64.7 (CH_2), 24.0 (CH(*C*H_3)$_2$), 21.8 (CH), 18.6 (CH), 12.6 (CH_2); *m/z* HRMS (+ESI) found: $[M+Na]^+$ 181.0839; $C_8H_{14}O_3Na$ requires 181.0835.

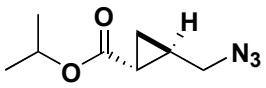
Isopropyl (1*R*, 2*R*)-2-{[(methylsulfonyl)oxy]methyl}cyclopropanecarboxylate 6



Triethylamine (7.6 g, 50.6 mmol) and methane sulfonylchloride (4.7g, 41.1 mmol) were added to a stirred solution of cyclopropane alcohol **5a** (5.0 g, 31.6 mmol) in dichloromethane (35 mL) at 0°C. After 10 mins, TLC (EtOAc/petrol, 1:1) indicated complete conversion of starting material (R_f 0.47) to a single product (R_f 0.60). The reaction mixture was diluted with dichloromethane (150 mL) and washed with ammonium chloride (100 mL) and water (100 mL). The aqueous washes were extracted with dichloromethane (2 x 150 mL) and the organic layers combined, dried ($MgSO_4$), filtered and solvents removed *in vacuo*. The residue was purified by flash column chromatography (EtOAc/petrol, 3.5:6.5) to yield the mesylated product **6** (6.7 g, 28.4 mmol, 90 %) as a colourless oil.

R_f 0.30 (EtOAc/petrol, 3.5:6.5); $[\alpha]_D^{25}$ = 50.2 (38.6 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 1714 (C=O str), 1455, 1418, 1166, 1111; δ_H (400 MHz, $CDCl_3$) 4.99 (1H, sept, J 6.3, C*H*$(CH_3)_2$), 4.17 (1H, dd, J 11.0, 6.9, H-5), 4.08 (1H, dd, J 11.0, 7.0, H5'), 3.03 (3H, s, C*H*$_3$), 1.87-1.79 (1H, m, H4), 1.65 (1H, ddd, J 8.9, 5.0, 4.1, H2), 1.32-1.27 (1H, m, H3'), 1.23 (3H, d, J 6.3, OCH(C*H*$_3$)(CH_3)), 1.22 (3H, d, J 6.3, OCH(CH_3)(C*H*$_3$)), 0.95 (1H, ddd, J 8.7, 6.0, 4.8, H3); δ_C (100 MHz, $CDCl_3$) 172.0 (C), 71.5 (CH_2), 68.3 (CH), 37.9 (CH_3), 21.8 (CH(*C*H_3)$_2$), 20.0 (CH), 19.3 (CH), 13.1 (CH_2). *m/z* HRMS (+ESI) found: $[M+Na]^+$ 259.0611; $C_9H_{16}O_5NaS$ requires 259.0610.

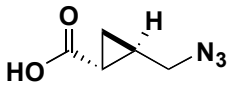
Isopropyl (1*R*, 2*R*)-2-(azidomethyl)cyclopropanecarboxylate 1



Sodium azide (2.4 g, 36.9 mmol) was added to a stirred solution of the mesylated product **6** (6.7 g, 28.4 mmol) in dimethylformamide (55 mL). The reaction mixture was heated at 95˚C for 3h when TLC (EtOAc/petrol, 1:1) indicated complete conversion of starting material (R_f 0.60) to a single product (R_f 0.92). The reaction mixture was diluted with water (125 mL), extracted with diethyl ether (3x100 mL) and the combined organic layers were washed with water (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/petrol, 1:16) to yield the azido ester **1** (3.8 g, 20.7 mmol, 73%) as a colourless oil.

R_f 0.31 (EtOAc/petrol, 1:16); $[\alpha]_D^{25}$ = 56.9 (10.2 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 2982 (CH), 2086 (N_3), 1717 (C=O), 1451, 1180, 1106; δ_H (400 MHz, $CDCl_3$) 5.0 (1H, sept, J 6.3, C*H*(CH_3)$_2$), 3.22 (2H, d, J 6.7, H5, H5'), 1.75-1.67 (1H, m, H4), 1.58-1.53 (1H, m, H2), 1.28-1.26 (1H, m, H3'), 1.24 (3H, d, J 6.3, OCH(C*H*$_3$)(CH_3)), 1.23 (3H, d, J 6.3, OCH(CH_3)(C*H*$_3$)), 0.87 (1H, ddd, J 8.5, 6.1, 4.6, H3); δ_C (100 MHz, $CDCl_3$) 172.5 (C), 68.1 (CH), 53.3 (CH_2), 21.8 (CH(*C*H_3)$_2$), 20.4 (CH), 18.9 (CH), 13.1 (CH_2). *m/z* HRMS (+ESI) found: $[M+Na]^+$ 206.0906; $C_8H_{13}O_2NaN_3$ requires 206.0899.

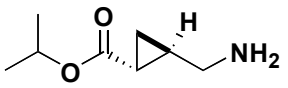
(1*R*, 2*R*)-2-(azidomethyl)cyclopropanecarboxylic acid 7



1 M Aqueous NaOH (104 mL, 104 mmol) was added to a stirred solution of azido ester **1** (3.8 g, 20.7 mmol) in ethanol (25 mL). The reaction was stirred at room temperature for 24 h, when TLC (EtOAc/petrol, 1:16) indicated complete conversion of starting material (R_f 0.34) to a major product (R_f 0-0.1). The solvent was removed under reduced pressure and the resulting residue was dissolved in de-ionized water (75 mL) and acidified to pH 2-3 with 3M aqueous HCl. The resulting mixture was extracted with dichloromethane (4 x 100 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the azido acid **7** (2.9 g, 20.5 mmol, 99%), which was used without further purification.

R_f 0.31 (EtOAc/petrol/AcOH, 3.5:6.5:0.1) $[\alpha]_D^{25}$ = 69.2 (20.4 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 2926, 2086 (N_3), 1690 (C=O), 1453; δ_H (400 MHz, $CDCl_3$) 3.28 (1H, dd, J 13.1, 6.5, H5), 3.22 (1H, dd, J 13.1, 6.8, H5') 1.83-1.75 (1H, m, H4), 1.61 (1H, ddd, J 8.8, 4.8, 4.1, H2), 1.36-1.32 (1H, m, H3'), 0.99 (1H, ddd, J 8.5, 6.4, 4.7, H3); δ_C (100 MHz, $CDCl_3$) 179.4 (C), 53.1 (CH_2), 21.5 (CH), 18.4 (CH), 13.9 (CH_2); *m/z* HRMS (ES+) found: $[M+NH_4]^+$ 159.0877; $C_5H_7N_3O_2$ requires 159.0878.

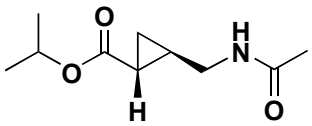
Isopropyl (1*R*, 2*R*)-2-(aminomethyl)cyclopropanecarboxylate 8



A deoxygenated solution of azido ester **1** (2.5 g, 13.6 mmol) in ethyl alcohol (20 mL) was added dropwise to a stirred, suspension of palladium black (10 wt %**,** 250 mg) in ethyl alcohol (15 mL) under an atmosphere of hydrogen. The reaction mixture was stirred under a hydrogen atmosphere for 30 mins when TLC (EtOAc/petrol, 1:16) indicated complete conversion of starting material (R_f 0.34) to a major product (R_f 0-0.1). The reaction mixture was filtered through Celite^{TM} (washing with ethanol) and concentrated *in vacuo* to yield the amine **8** (2.1 g, 13.3 mmol, 98%), which was used without further purification.

Rf 0.22 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = 59.5 (12 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 2981, 2934, 1715 (C=O str), 1453, 1175, 1106, 911, 874, 796; δ_H (400 MHz, $CDCl_3$) 4.96 (1H, sept, J 6.3, C*H*(CH_3)$_2$), 2.83 (2H, brs, NH_2), 2.70 (1H, dd, 12.0, 5.5, H5), 2.66 (1H, dd, 12.0, 5.5, H5') 1.62-1.54 (1H, m, H4), 1.49-1.44 (1H, m, H2), 1.22 (3H, d, J 6.3, OCH(C*H*$_3$)(CH_3)), 1.21 (3H, d, J 6.3, OCH(CH_3)(C*H*$_3$)), 1.19-1.15 (1H, m, H3'), 0.79 (1H, ddd, J 8.5, 6.4, 4.7, H3); δ_C (100 MHz, $CDCl_3$) 173.4 (C), 67.6 (*C*H(CH_3)$_2$), 45.1 (CH_2), 25.6 (CH), 21.8 (CH(*C*H_3)$_2$), 19.1 (CH), 13.5 (CH_2).

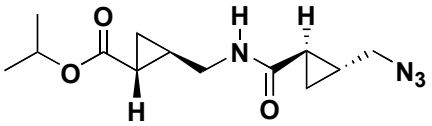
Isopropyl (1*R*, 2*R*)-2-(*N*-acylaminomethyl)cyclopropanecarboxylate 8a



Acetic anhydride (1mL) was added to a stirring solution of amine **8** (100 mg, 0.64 mmol) in pyridine (1mL). After one hour at room temperature, the mixture was concentrated and residue was purified by flash column chromatography ($CHCl_3$/methanol, 9:1) to yield the amide **8a** (52 mg, 0.26 mmol, 40%).

Rf 0.33 ($CHCl_3$/MeOH, 9:1); $[\alpha]_D^{25}$ = 66.7 (20 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3283 (NH), 3083, 2980, 2936, 1718 (ester C=O), 1649 (Amide I) 1548 (Amide II), 1451, 1366, 1180, 1105; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, s, NH), 4.93 (1H, sept, J 6.3, C*H*(CH_3)$_2$), 3.22-3.11 (2H, m, H5, H5'), 1.95 (3H, s, COC*H*$_3$), 1.59-1.51 (1H, m, H4), 1.46 (1H, td, J 8.7, 4.4, H2), 1.19 (3H, d, J 6.3, OCH(C*H*$_3$)(CH_3)), 1.18 (3H, d, J 6.3, OCH(CH_3)(C*H*$_3$)), 1.13 (1H, td, J 8.9, 4.6, H3'), 0.79 (1H, ddd, J 8.5, 6.2, 4.4, H3); δ_C (100 MHz, $CDCl_3$) 172.9 (C), 170.0 (C), 67.8 (CH), 42.0 (CH_2), 23.0 (CH(*C*H_3)$_2$), 21.7 (CH_3), 21.4 (CH), 19.2 (CH), 13.6 (CH_2).). *m/z* HRMS (+ESI) found: $[M+H]^+$ 200.1287; $C_{10}H_{18}O_5N$ requires 200.1281.

Isopropyl (1*R*, 2*R*)-2-[({[(1*R*, 2*R*)-2-(azidomethyl)cyclopropyl]carbonyl}amino)-methyl]cyclopropanecarboxylate 9[1]



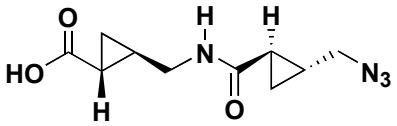
TBTU (3.37g, 10.5 mmol) and diisopropylethylamine (1.83 mL, 10.5 mmol) were added to a stirred solution of the azido acid **7** (825 mg, 5.25 mmol) and amino ester **8** (825 mg, 5.84 mmol) in CH_2Cl_2/ dimethylformamide (2:1 v/v, 6 mL). After 24 h at room temperature, TLC (EtOAc/petrol, 2:1) indicated almost complete conversion of the starting materials (R_f 0-0.1) to a major product (R_f 0.34). The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane (30 mL). The solution was washed with 3M HCl (10 mL) and pH 7 buffer (10 mL). The collected aqueous layers were extracted with dichloromethane (20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/petrol, 2:1) to yield the dimer **9** (985 mg, 3.51 mmol, 73.5%) as a colourless solid.

R_f 0.34 (diethyl ether/petroleum ether 40-60, 2:1); m.p. 54-55˚C; $[\alpha]_D^{25}$ = 62.2 (17.9 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3302 (NH), 2982, 2935, 2089 (N_3), 1716 (ester C=O), 1643 (Amide I), 1547 (Amide II), 1450, 1181, 1106; *m/z* HRMS (ES+) found 281.1608; $C_{13}H_{20}N_4O_3$ $[M+H]^+$ requires 281.1610.

Residue	Position		δ_H (500 MHz, $CDCl_3$)	Multiplicity	J (Hz)	δ_C (125 MHz, $CDCl_3$)
A	C-1		-	-	-	171.6
	C-2		1.36-1.32	m	-	20.5
	C-3	3	0.77	ddd	8.3, 5.9, 4.8	13.6
		3’	1.26-1.23	m	-	
	C-4		1.72-1.66	m	-	19.5
	C-5	5	3.31	dd	13.0, 6.1	53.4
		5’	3.11	dd	13.0, 7.4	
B	C-1		-	-	-	172.9
	C-2		1.50-1.47	m	-	19.3
	C-3	3	0.81	ddd	8.6, 6.2, 4.7	11.9
		3’	1.18-1.14	m	-	
	C-4		1.61-1.55	m	-	21.5
	C-5	5,5’	3.21, (2H)	t	6.3	42.3
	NH		5.99	brs	-	-
i-Pr	C		4.96	sept	6.2	67.9
	Me		1.20 (3H)	d	6.2	21.8
	Me		1.21 (3H)	d	6.2	

[1] Individual residues in these oligomeric materials may be identified alphabetically, from the *N*-to the *C*-terminus.

(1*R*, 2*R*)-2-{[((1*R*, 2*R*)-2-azidomethyl-cyclopropanecarbonyl)-amino]-methyl}-cyclopropanecarboxylic acid 9a

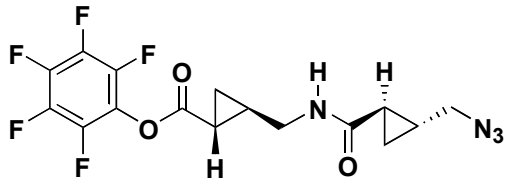


1 M Aqueous NaOH (2.28 mL, 2.28 mmol) was added to a stirred solution of dimeric azido ester **9** (128 mg, 0.46 mmol) in ethanol (1 mL). The reaction was stirred at room temperature for 24 h, when TLC (EtOAc/petrol, 2:1) indicated complete conversion of starting material (R_f 0.36) to a major product (R_f 0-0.1). The solvent was removed under reduced pressure and the resulting residue was dissolved in distilled water (10 mL) and acidified to pH 2-3 with 3M aqueous HCl. The resulting mixture was extracted with dichloromethane (4 x 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the dimeric azido acid **9a** (109 g, 0.45 mmol, 99%) as a colourless solid which was used without further purification.

R_f 0.13 ($CHCl_3$/MeOH, 9:1); m.p. 62˚C; $[\alpha]_D^{25}$ = 64.2 (3.3 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3293, 2933, 2090 (N_3), 1697 (C=O), 1629 (Amide I), 1547 (Amide II), 1423; 1226, 1189; *m/z* HRMS (ES+) found 239.1139; $C_{10}H_{14}N_4O_3$ $[M+H]^+$ requires 239.1139

Residue	Position		δ_H (500 MHz, $CDCl_3$)	multiplicity	J (Hz)	δ_C (125 MHz, $CDCl_3$)
A	C-1		-	-	-	178.6
	C-2		1.54	td	8.6, 4.5	20.5
	C-3	3	0.91	ddd	8.3, 6.3, 4.6	14.2
		3’	1.29-1.24	m	-	
	C-4		1.68-1.62	m	-	22.5
	C-5	5	3.39-3.31	m	-	42.4
		5’	3.15-3.05	m	-	
B	C-1		-	-	-	171.8
	C-2		1.37	td	8.6, 4.5	19.3
	C-3	3	0.80	ddd	8.3, 5.9, 4.6	12.1
		3’	1.29-1.24	m	-	
	C-4		1.75-1.69	m	-	19.6
	C-5	5	3.39-3.31	m	-	53.4
		5’	3.15-3.05	m	-	
	NH		6.06	t	5.3	-

Pentafluorophenyl (1*R*, 2*R*)-2-[({[(1*R*, 2*R*)-2-(azidomethyl)cyclopropyl]carbonyl}amino)-methyl]cyclopropanecarboxylate 10



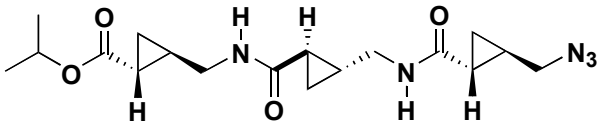
A solution of pentafluorophenol (125 mg, 0.68 mmol) in dichloromethane (0.5 mL) was added dropwise to a stirred solution of azido acid **9a** (109 mg, 0.45 mmol) and EDCI (105 mg, 0.68 mmol) in dichloromethane (1 mL). The reaction mixture was sonicated for 30 mins when TLC (EtOAc/petroleum ether 40-60, 3.5:6.5) indicated complete conversion of starting material (R_f 0-0.1) to a single product (R_f 0.25). The reaction mixture was concentrated and the residue was subjected to flash column chromatography (EtOAc/petroleum ether 40-60, 4.0:6.0) to yield the ester **10** (135 mg, 0.33 mmol, 73%) as a colourless solid.

R_f 0.3 (EtOAc/petroleum ether 40-60, 2:3); m.p. 48˚C; $[\alpha]_D^{25}$ = 73.1 (30 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3304, 2928, 2097 (N_3), 1769 (C=O), 1639 (Amide I), 1518 (Amide II), 1358; 1126, 989; *m/z* HRMS (ES+) found 427.0800; $C_{16}H_{13}F_5N_4O_3$ $[M+H]^+$ requires 427.0801.

Residue	Position		δ_H (500 MHz, $CDCl_3$)	multiplicity	J (Hz)	δ_C (125 MHz, $CDCl_3$)
A	C-1		-	-	-	171.9
	C-2		1.38	td	8.5, 4.5	20.5
	C-3	3	0.81	ddd	8.3, 6.1, 4.6	12.0
		3’	1.29-1.23	m	-	
	C-4		1.75-1.68	m	-	19.7
	C-5	5	3.10	dd	11.1, 7.5	53.3
		5’	3.38-3.28	m	-	
B	C-1		-	-	-	169.6
	C-2		1.91-1.88	m	-	17.9
	C-3	3	1.15	ddd	8.4, 6.6, 4.8	15.3
		3’	1.43	td	9.2, 4.8	
	C-4		1.87-1.81	m	-	23.9
	C-5	5,5’	3.38-3.28 (2H)	m	-	41.8
	NH		6.18	t	5.2	-
C_6F_5[2]	C		-	-	14.5 (t)	120.5
	CF				251.4 (dm)	141.1
	CF				253.3 (dm)	139.4
	CF				254.2 (dm)	137.8

[2] The ^{13}C signals for the pentafluorophenol are complex (and unresolved at this field strength), but we have quoted the chemical shifts as the centre of the multiplet patterns, described some of these patterns as ‘dm’ (doublets of multiplets) and quoted the larger $^1J_{C,F}$ coupling constant for information.

Isopropyl (1*R*, 2*R*)-(2-{[((1*R*, 2*R*)-2-{[(1*R*, 2*R*)-(2-azidomethyl-cyclopropanecarbonyl)-amino]-methyl}-cyclopropanecarbonyl)-amino]-methyl}-cyclopropanecarboxylate 3



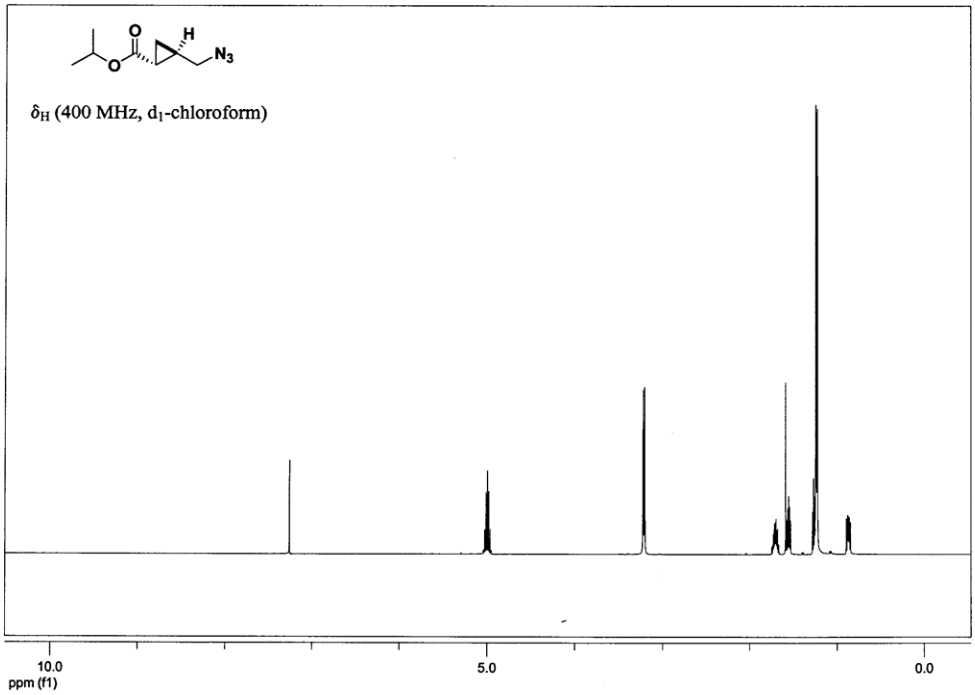
A solution of amino ester **8** (63 mg, 0.40 mmol) in dichloromethane (0.5 mL) was added dropwise to a stirring suspension of pentafluorophenol ester **10** (135 mg, 0.33 mmol), HOBT (2.0 mg, 0.015 mmol) and Na_2CO_3 (277 mg, 3.3 mmol) in dichloromethane (1 mL). After 18h, TLC (R_f 0.3, EtOAc/petroleum ether 40-60, 4.0:6.0) indicated the consumption of starting material **8**. The mixture was concentrated under vacuum and the residue was subjected to flash column chromatography ($CHCl_3$/methanol, 9:1) to yield the trimeric azido ester **3** (44 mg, 0.12 mmol, 80%) as a colourless solid.

R_f 0.24 ($CHCl_3$/MeOH, 9:1); m.p. 186˚C; $[\alpha]_D^{25}$ = 112.7 (3.3 mg in 2 mL $CHCl_3$); ν_{max} /cm^{-1} (film): 3303 (NH), 2982, 2879, 2098 (N_3), 1711 (ester C=O), 1627 (Amide I), 1547 (Amide II), 1451, 1203, 1106.; *m/z* HRMS (ES+) found 378.2136; $C_{18}H_{27}N_5O_4$ $[M+H]^+$ requires 378.2140.

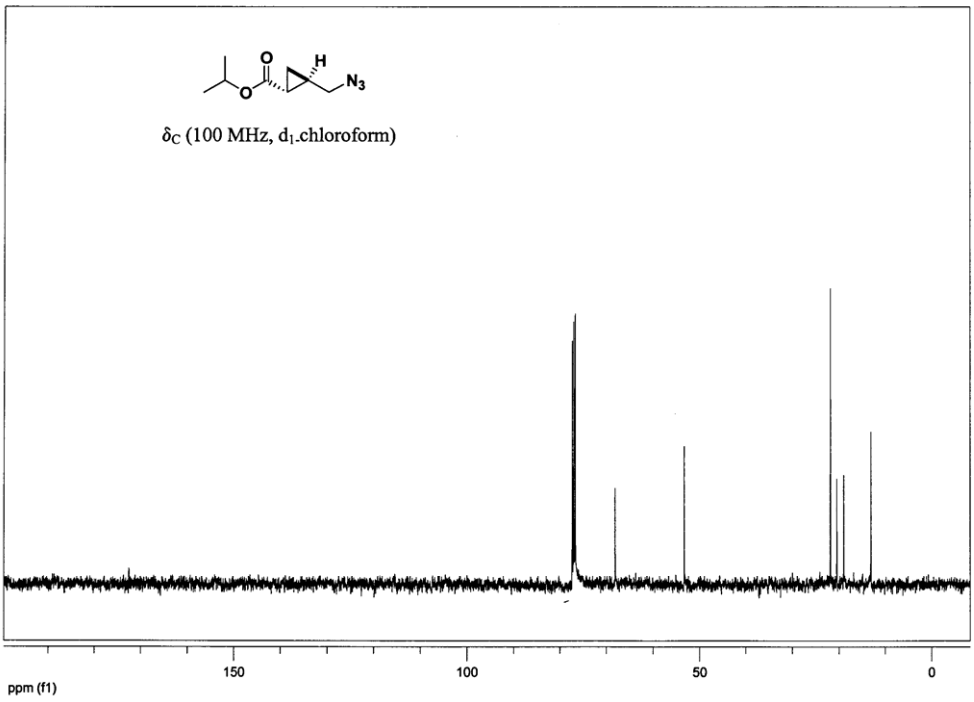
RING	Position		δ_H (700 MHz, $CDCl_3$)	multiplicity	J (Hz)	δ_C (125 MHz, $CDCl_3$)
A	C-1		-	-	-	171.8
	C-2		1.39-1.34	m	-	20.6
	C-3	3	0.79	ddd	8.3, 6.1, 4.6	12.0
		3’	1.26-1.24	m	-	
	C-4		1.72-1.68	m	-	19.6
	C-5	5	3.32	dd	13.0, 6.1	53.4
		5’	3.12	dd	13.0, 7.4	
B	C-1		-	-	-	172.2
	C-2		1.39-1.34	m	-	19.3
	C-3	3	0.75	ddd	8.3, 6.0, 4.4	12.4
		3’	1.19-1.15	m	-	
	C-4		1.56-1.52	m	-	21.3
	C-5	5,5’	3.26-3.18 (2H)	m	-	42.3
	NH		5.93-5.91	m	-	-
C	C-1		-	-	-	173.0
	C-2		1.50-1.48	m	-	20.6
	C-3	3	0.82	ddd	8.7, 6.3, 4.6	13.7
		3’	1.19-1.15	m	-	
	C-4		1.61-1.56	m	-	21.4
	C-5	5,5’	3.26-3.18 (2H)	m	-	42.5
	NH		5.93-5.91	m	-	-
i-Pr	C		4.98	sept	6.3	67.9
	Me		1.23 (3H)	d	7.6	21.8
	Me		1.24 (3H)	d	7.6	

3. Proton and carbon NMR spectra for compounds 1, 9 and 3.

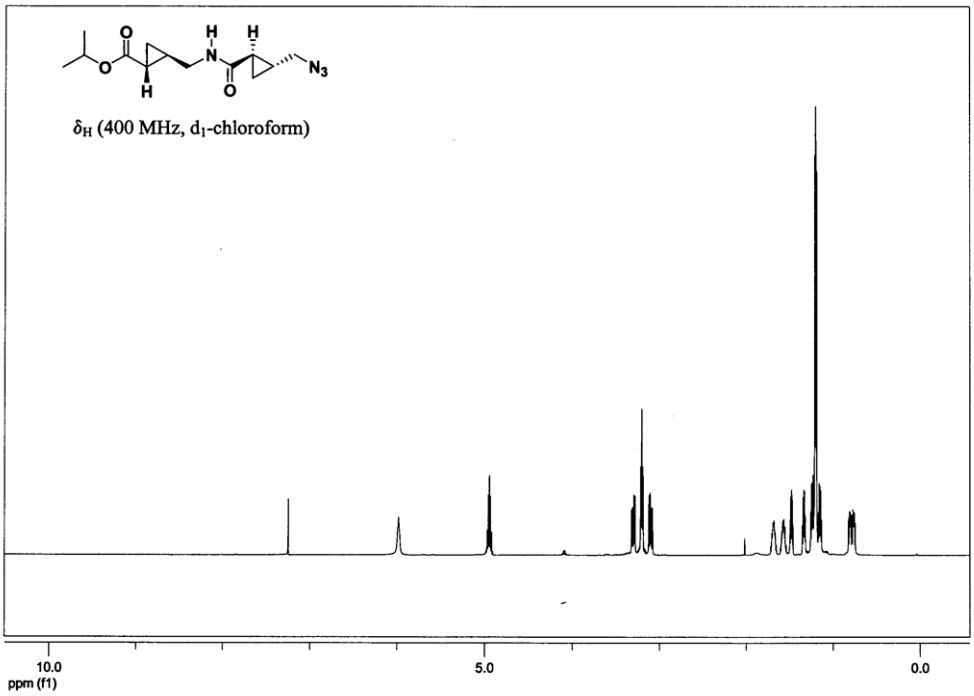
Compound 1 - ^{1}H:



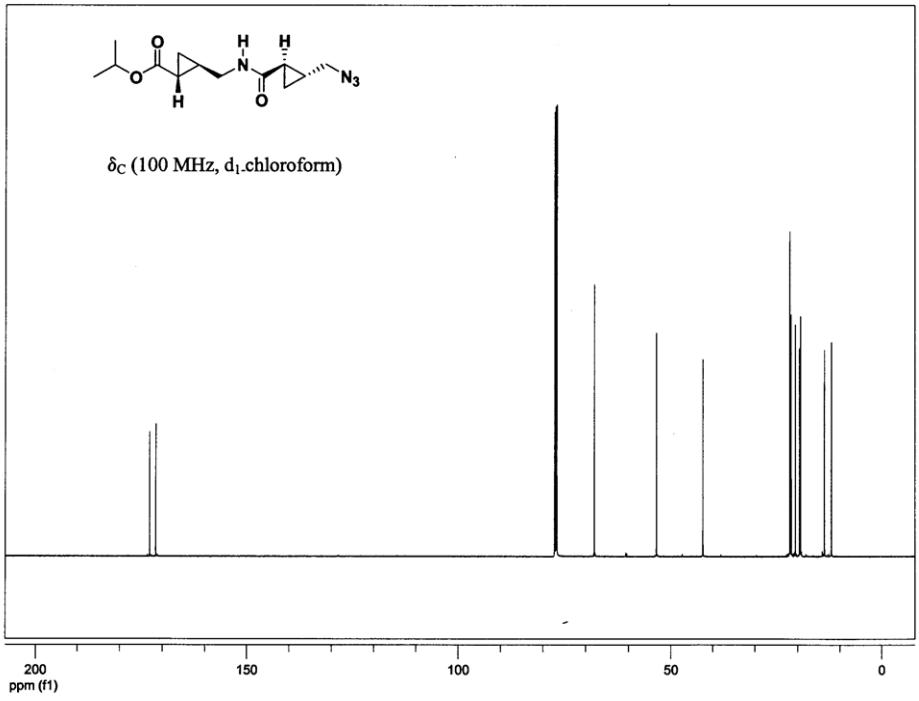
Compound 1 - ^{13}C:



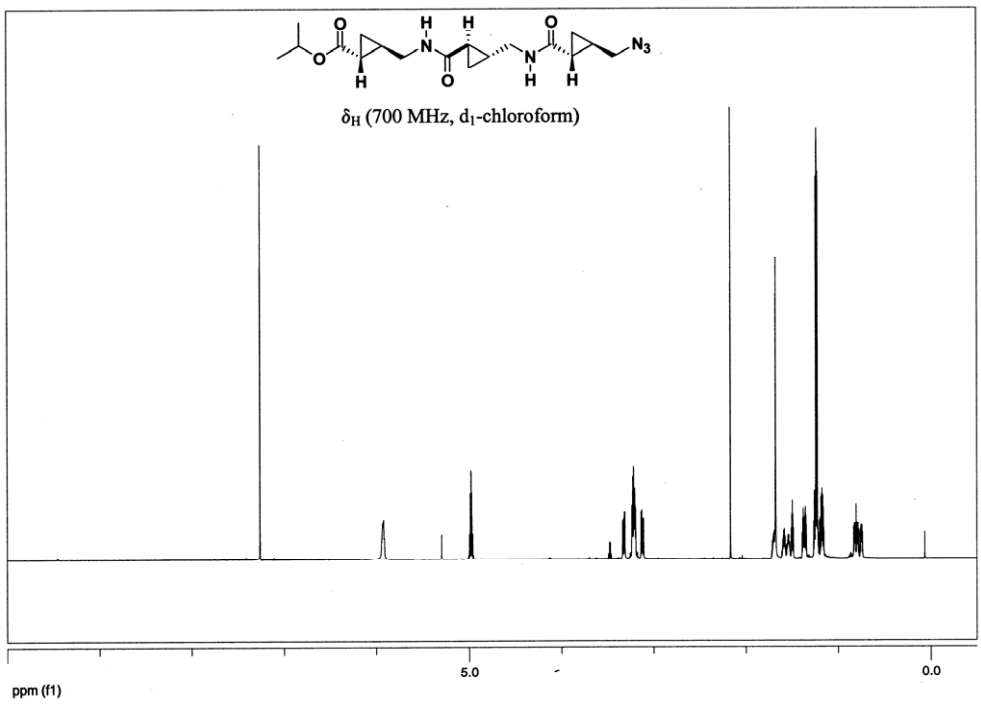
Compound 9 - ^{1}H



Compound 9 - ^{13}C



`Compound 3 - ^{1}H:



Compound 3 - ^{13}C