1 PERKIN

Tetrahydrofuran amino acids: Secondary structure in tetrameric and octameric carbopeptoids derived from a D-*allo* 5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid

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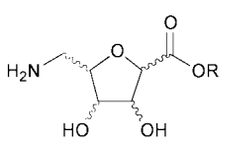
The synthesis of a D-*allo*-5-(azidomethyl)tetrahydrofuran-2-carboxylate as an amino acid precursor (in which the carboxylic acid is *cis* to the azidomethyl substituent and *trans* to the diol moiety) is reported from D-ribose. The oligomerisation of this monomer to dimeric, tetrameric and octameric carbopeptoids is described. NMR studies into the solution structures of cyclohexylidene-protected oligomers and of a deprotected tetramer with eight free hydroxy groups are described.

Introduction

Peptidomimetics constitute rigid templates with the ability to exhibit conformational influences on the peptide backbone; the preceding paper describes the synthesis of oligomers of an all-*cis*-THF amino acid monomer in which there is essentially no evidence for significant secondary structure arising from the THF template.[1] Dipeptide analogues can be generated by substitution of the amide bond with an isosteric unit. Such replacement often increases the metabolic stability of peptide-based drugs. If the isosteric unit is stereochemically constrained then the conformational possibilities are limited compared with that of the regular dipeptide. Carbohydrate-derived tetrahydrofuran amino acids (*e.g.*, **1**) have been employed as conformationally restricted dipeptide isosteres. Structure **1** can be likened to a conventional dipeptide **2** in which the ether linkage replaces the amide bond and rigidly links the two amino acids.[2] For example, a tetrahydrofuran sugar amino acid was incorporated into Leu-enkephalin as a Gly-Gly substitute.[3] When linked together into oligomers these compounds constitute a subset of 'carbopeptoids'.[4] Different substitution patterns around the tetrahydrofuran ring and changes in backbone stereochemistries lead to oligomers which display different secondary structures in solution. For instance, different diastereomers of **1** form β-turn[5] and left-handed helical[6] solution structures. Thus the set of different stereoisomers of the 5-(aminomethyl)tetrahydrofurancarboxylic acid **1** scaffold show promise as dipeptide isostere building blocks that are predisposed towards different secondary structures[2] and perhaps will lead one day to an increased understanding of foldamers.[7]

The ability to readily deprotect or derivatise the polyhydroxy function of carbohydrate-derived oligomers opens the possibility of creating peptide mimics possessing hydrophobic or hydrophilic properties. This is of interest, considering protein secondary structures are determined by such interactions.[8]

This paper describes the efficient synthesis of a stereoisomer of tetrahydrofuran amino acid **1**, initially as a protected form of the azido ester **3** (with D-*allo* configuration), and its conversion to homooligomers,[6] including the protected dimer **4**, tetramer **5** and octamer **6**, with the latter two exhibiting evidence of secondary structure in solution. The D-*allo* stereochemistry of **3** with the 3,4-*cis*-diol unit permits efficient protection of these systems with ketal protecting groups, providing readily manageable oligomeric materials, while deprotection of the ketals affords water-soluble compounds such as the dimer **7** and tetramer **8**. The structure of the deprotected tetramer (with eight free hydroxy groups) is also examined in solution.



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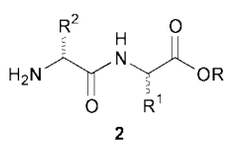

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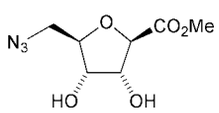

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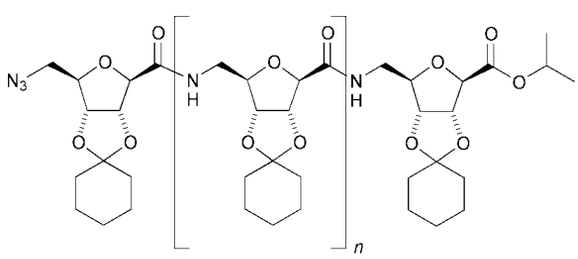
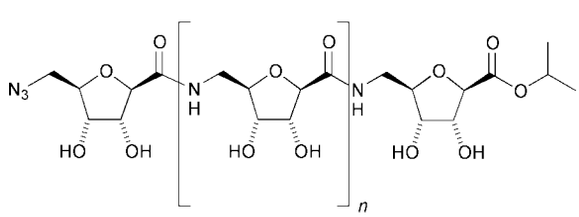


4 *n* = 0, cyclohexylidene dimer
5 *n* = 2, cyclohexylidene tetramer
6 *n* = 6, cyclohexylidene octamer



7 *n* = 0, dimer
8 *n* = 2, tetramer

Results and discussion

Tetrahydrofuran-2-carboxylates are generally and readily accessible *via* acid- or base-catalysed ring rearrangements of 2-*O*-trifluoromethanesulfonate derivatives of carbohydrate

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lactones.[9,10] The key step in this conversion to tetrahydrofuran *C*-glycosides involves treatment of the 2-*O*-triflate derivative of the lactone with acidic or basic methanol, conditions which result in methanolysis of the lactone and intramolecular S_N2 displacement of the triflate by 5-OH. In the synthesis of the D-*talo*-THF azido ester **10** by a base-catalysed ring contraction of the 2-*O*-triflate of the azido lactone **9**, the L-*allo* tetrahydrofuran amino acid **11** (enantiomeric to **3**) was obtained[11] as a minor product (13%) (Scheme 1); inversion of configuration occurred at both C-2 and C-5 in the transformation of **9** to **11**. The minor product **11** was subsequently protected and homo-oligomerised to the dimer and tetramer in which initial studies indicated that such materials might have secondary structure arising from intramolecular hydrogen bonding.[6]

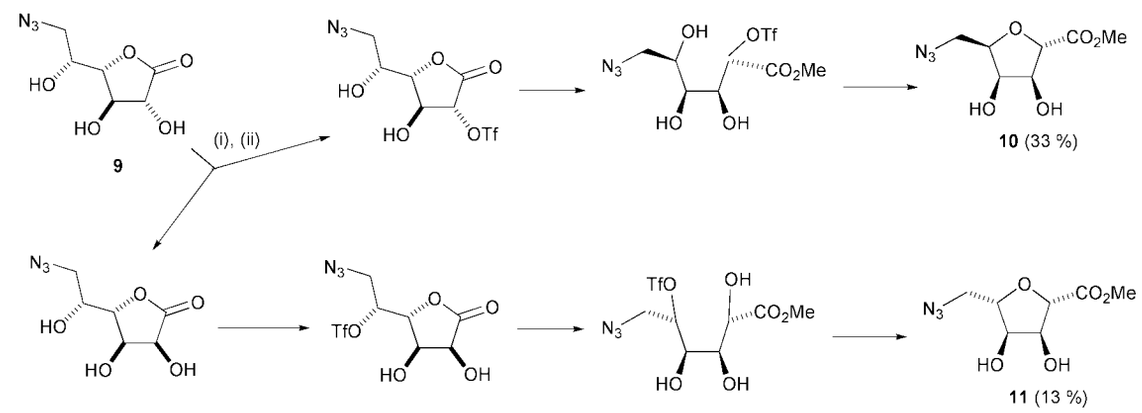
Synthesis of protected building blocks of the monomer 3

A direct and unambiguous synthesis of an *allo*-configured equivalent of the amino acid **3** was required for further studies of these homooligomers and this paper reports the synthesis of a protected form of **3** (P) = (H), the enantiomer of **11**, from D-ribose. The alternative strategies for the formation of **3** are shown in Scheme 2 in which the azide may be introduced prior – or subsequent – to the generation of the THF ring; in both cases the THF ring is formed by triflate displacement by the C-5 oxygen with inversion of configuration at C-2 of a suitable protected δ-lactone with D-*altro* stereochemistry. The common starting material for both routes is the cyclohexylidene sugar lactone **12** accessible *via* the Kiliani ascension on 2,3-*O*-cyclohexylidene-D-ribose;[12] the cyclohexylidene ketal is more accessible than the corresponding acetonide.[13,14]

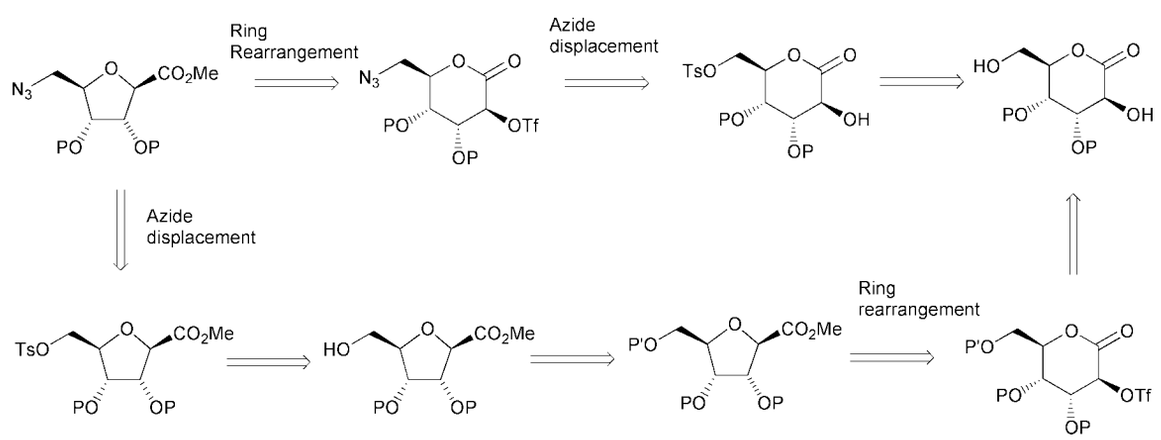
The most attractive route to a protected equivalent of the D-*allo* ester **3** involved introduction of azide prior to THF ring formation; this would avoid the need to protect the 6-OH and hence remove a protection/deprotection sequence. The diol **12** was therefore treated with 1 equivalent of tosyl chloride in pyridine to give the corresponding tosyl ester at C-6 **13** in 61% yield (Scheme 3), together with a small amount of the ditosyl compound **14**. Treatment of the monotosyl derivative **13** with sodium azide in dimethylformamide (DMF) at 70 °C produced only a small amount of the required azide **15** and gave the 2,6-anhydro-lactone **16** as the major product by base-catalysed elimination of tosic acid. The spectroscopic data for **15**[15] and **16**[16] obtained were in accord with their reported values.

It was thus clear that it was necessary to generate the THF ring prior to introduction of the azide. However, it was considered that in the current synthesis in which azide was to be introduced at C-6, a protection/deprotection sequence at 6-OH could be avoided if the 6-*O*-tosyl ester was employed as a temporary protecting group during the ring contraction, subsequently being displaced by azide. Thus, treatment of C-6 tosyl ester **13** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine in dichloromethane (DCM) resulted in the isolation of 2-*O*-triflate **17** (Scheme 4), which was immediately treated with potassium carbonate in methanol to yield D-*allo*-tetrahydrofuran **19**, with the C-6 tosyl ester intact. A small amount of the D-*altro* product **20** was also formed. Subsequent reaction of **19** with sodium azide in DMF resulted in displacement of the tosyl ester to afford the azido ester **18** in 92% yield (32% overall yield in 4 steps from the lactone diol **12**).

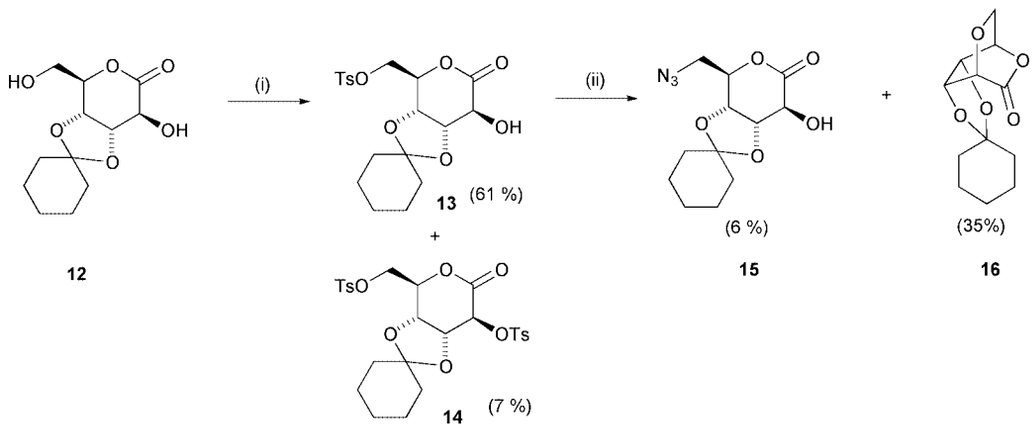
A shorter sequence to the target azido ester **18** could be achieved if the 2,6-di-*O*-tosyl lactone **14** formed the THF tosyl ester **19** on treatment with basic methanol; this would avoid both the need for a selective tosylation of the 6-OH in **12** as well as the use of the relatively expensive triflic anhydride. Treatment of the diol **12** with an excess of tosic anhydride gave the ditosyl compound **14** in 89% yield. When the ditosyl compound **14** was treated with potassium carbonate in methanol, the required D-*allo* tetrahydrofuran tosyl ester **19** was obtained as the major product in 56% yield, together with the D-*altro* epimer **20** in 6%



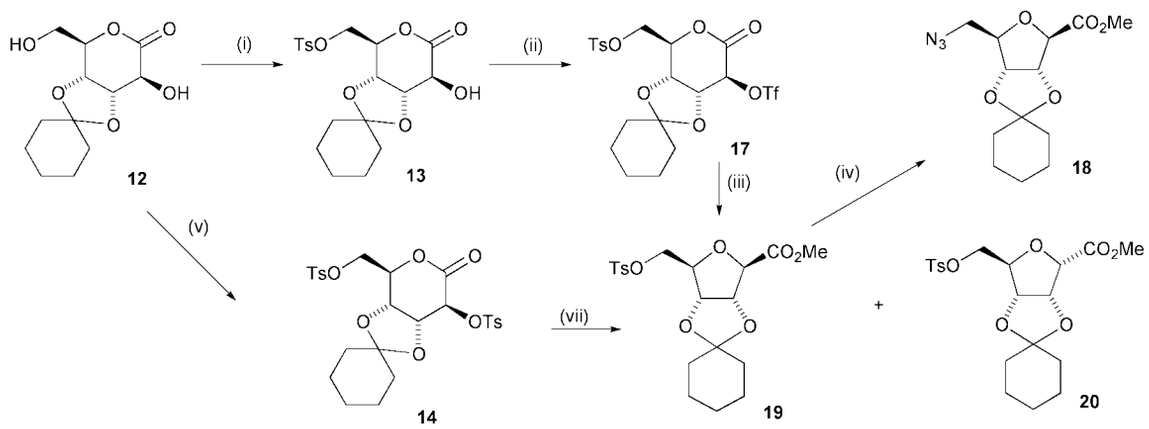
Scheme 1 *Reagents and conditions*: (i) Tf_2O, pyridine, ethyl acetate, −10 °C; (ii) MeOH.



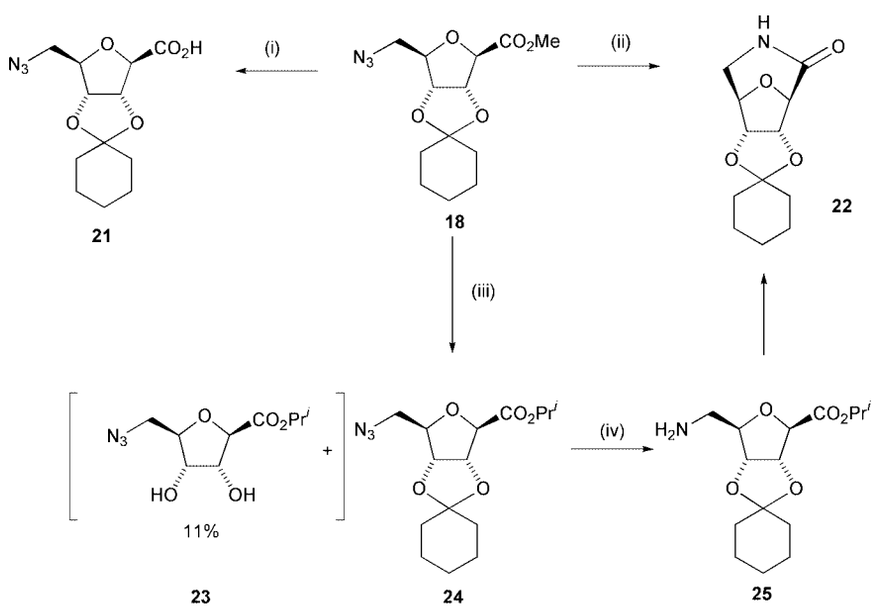
Scheme 2



Scheme 3 *Reagents*, *conditions and yields*: (i) 1 eq. *p*TsCl, py, 16 h (61%) (ii) NaN_3, DMF, 16 h, 70 °C.



Scheme 4 *Reagents*, *conditions and yields*: (i) 1 eq. *p*TsCl, py, 16 h (61%) (ii) Tf_2O, py, −40 to −20 °C, DCM (85%) (iii) K_2CO_3, MeOH (67%) (2 steps) (iv) NaN_3, DMF, 85 °C, 2 h (92%) (v) excess of pTs_2O, py, 16 h (89%) (vii) K_2CO_3, MeOH, 1 h (56%).



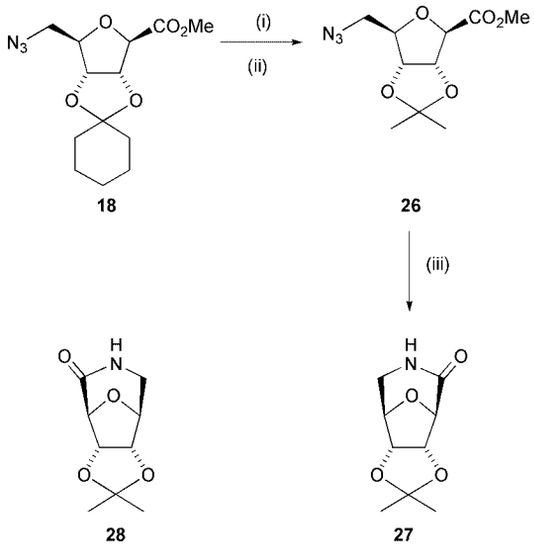
Scheme 5 *Reagents*, *conditions and yields*: (i) aq. NaOH, 1,4-dioxane, 1 h; then Amberlite IR-120 (H^+) (ii) H_2, Pd black, MeOH, 1 hour (iii) H^+, Pr^iOH, 80 °C, 3 h (83%) (iv) H_2 Pd black, ^iPrOH, 30 min.

yield. Again subsequent azide displacement of 6-*O*-tosyl group in **19** yielded **18** in 92% yield (and in 3 steps from protected sugar lactone **12** in 46% overall yield).

Hydrolysis of the azido ester **18** with aq. sodium hydroxide gave the azido acid **21** as the *N*-protected monomeric acid component for oligomer formation (Scheme 5). Hydrogenation of methyl ester **18** gave the bicyclic lactam **22** in 64% yield. It was necessary to exchange the methyl for the more hindered isopropyl ester to produce an amine sufficiently stable to act as the *C*-protected component for oligomerisation studies. Accordingly, the methyl ester **18** was treated with a solution of HCl in propan-2-ol to give the isopropyl ester **24** in 83% yield; the diol **23** which arose from acid-catalysed loss of the cyclohexylidene protecting group was isolated in 11% yield. Hydrogenation of this azido isopropyl ester **24** in propan-2-ol in the presence of palladium black gave the corresponding amine **25**, which on

storage or on concentration of the solvent spontaneously formed the lactam **22**. However, the crude amine **25** in solution was used directly in the coupling reactions.

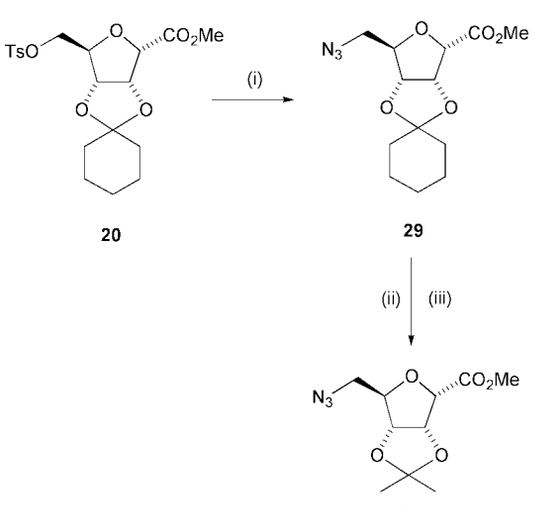
Structural proof of the D-*allo* stereochemistry for azido ester **18** was obtained by conversion to the isopropylidene lactam **27** (Scheme 6) for comparison with the reported enantiomeric



Scheme 6 *Reagents*, *conditions and yields*: (i) 40% aq. TFA, 1 h (ii) 2,2-DMP, acetone, CSA, 2 h; (iii) Pd black, H_2, MeOH, 1 h (68%) (over 3 steps).

lactam **28**.[6,11] Removal of the protecting groups in **18** with aq. trifluoroacetic acid (TFA) followed by treatment of the crude product with 2,2-dimethoxypropane (2,2-DMP) in acetone in the presence of (±)-camphorsulfonic acid (CSA) gave the isopropylidene methyl ester **26**. Hydrogenation of the azide **26** in methanol in the presence of palladium black afforded the lactam **27** in 68% overall yield and with spectroscopic data (^{1}H and ^{13}C NMR) identical with its enantiomer **28**,[11] but with the opposite sign for the specific rotation.

Proof of structure of the minor product **20** obtained in the ring-rearrangement procedure was provided by conversion to the known isopropylidene protected 6-azido altronate **30** (Scheme 7); **30** has been prepared in 8 steps from D-*allono*-1,4-



Scheme 7 *Reagents*, *conditions and yields*: (i) NaN_3, DMF, 90 °C, 2 h (70%) (ii) 40% aq. TFA, 24 h; (iii) 2,2-DMP, acetone, CSA, 16 h (31%) (over 2 steps).

lactone.[17] Treatment of the tosyl ester **20** with sodium azide in DMF at 90 °C for 2 h afforded the azide **29** in 70% yield. Treatment of the cyclohexylidene azide **29** with aq. TFA, followed by 2,2-DMP in acetone in the presence of CSA, gave the acetonide **30** with identical physical properties to those previously reported.[17]

Synthesis of protected and deprotected oligomers of 3

Homooligomerisation of the *allono* THF azido ester **18** was conducted *via* an iterative solution-phase sequence.[18] The D-*allo* acid **21** and amine **25** were coupled (Scheme 8) with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI)[19] and 1-hydroxybenzotriazole (HOBt)[20] in the presence of diisopropylethylamine (DIPEA) in dichloromethane to give the dimer **4** in 73% yield, together with the lactam **22** (derived from the cyclisation of **25**) in 14% yield.

Repetition of this procedure for the dimer **4** (azide reduction to give the amine **32** and ester hydrolysis to afford the acid **31** with subsequent coupling in the presence of EDCI, HOBt and DIPEA in dichloromethane) allowed the isolation of the tetramer **5** in 65% yield. An analogous procedure (involving reduction of the azide moiety in tetramer **5** to give amine **34** and hydrolysis to give the acid **33** followed by the coupling protocol) afforded the octamer **6** in 52% yield.

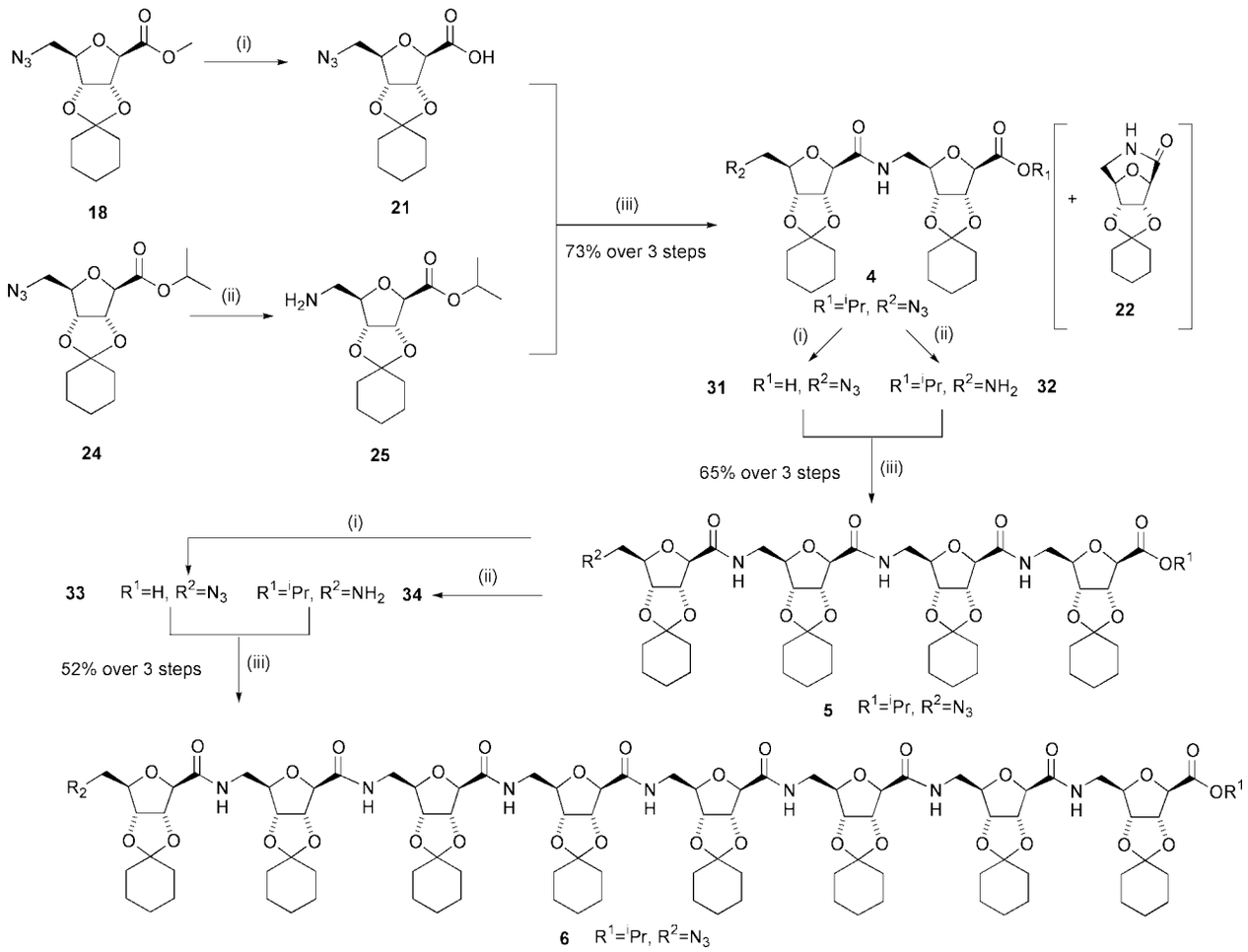
The ^{13}C isotope distribution provides strong evidence for the constitutional formula of compounds containing a high number of carbon atoms (*e.g.* C_{51} for tetramer **5** and C_{99} for octamer **6**); ^{13}C isotope constitutes 1.1% of carbon and so for a compound containing over 100 carbon atoms the base peak of the mass spectrum is shifted one Dalton higher. The experimental isotope distribution (positive-ion electrospray) observed matched the calculated distribution for each oligomeric material. All the cyclohexylidene oligomers were readily soluble in organic solvents and could be purified by conventional flash chromatography

Removal of the protecting groups in these oligomers should permit solubility in aqueous solutions and an examination of any secondary structures formed in such an environment. The cyclohexylidene protecting groups could be efficiently removed from the dimer **4** and tetramer **5** without any significant decomposition of the materials by reaction with trifluoroacetic acid in a mixed solvent system of chloroform, propan-2-ol and water to give the deprotected dimer **7** and the deprotected tetramer **8** in yields of 81 and 100%, respectively (Scheme 9).

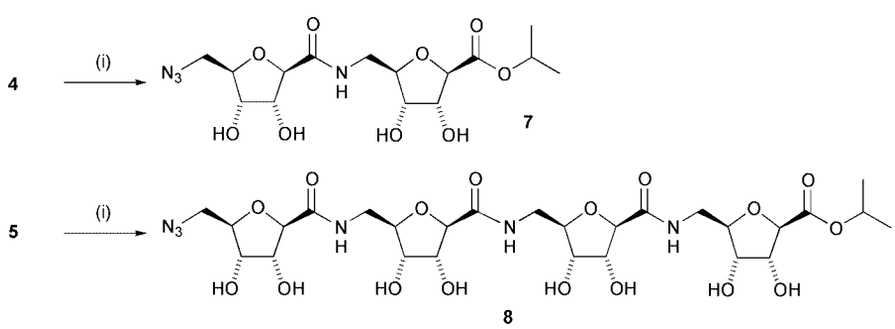
NMR and IR studies on protected and deprotected oligomers of 3

The solution secondary structural characteristics of the protected tetramer **5** and octamer **6**, and unprotected tetramer **8** were conducted by NMR spectroscopy, and compared with similar studies on the per-acetylated tetramer (with a *trans* secondary diol unit **35**) and with the acetonide **36**, enantiomeric with respect to the sugar component of the tetramer **5**.

A comparison of the $CDCl_3$ spectra of the protected tetramer **5** and octamer **6** is shown in Fig. 1. In the proton spectra of both the tetramer **5** and the octamer **6**, good proton dispersion for the sugar-ring protons was observed despite the repeating monomer units. In addition for both oligomers, one low-frequency amide proton ($\delta \approx 7.2$) was observed with the others resonating between δ 8.0–8.8, a chemical-shift range in $CDCl_3$ characteristic of amide protons involved in hydrogen bonding.[21] The low-frequency proton in each case was observed to be the *N*-terminal NH residue (NH_B)[22] which is not able to H-bond to the carbonyl of a preceding residue. Additional evidence for such H-bond formation is evident in the $CDCl_3$ solution IR spectra in which the tetramer **5** displays a sharp band at 3415 cm^{-1} characteristic of the N–H stretch of a free, solvated amide together with a broader band at 3320 cm^{-1} characteristic of an H-bonded amide proton.[23] Similarly, the octamer **6** displays bands at 3415 cm^{-1} (sharp) and 3299 cm^{-1} (broad) for which the intensity of the lower-frequency band relative to the higher is proportionately greater than that observed for the tetramer **5** (Fig. 2), consistent with the amide-



Scheme 8 *Reagents and conditions*: (i) aq. NaOH, 1,4-dioxane; then Amberlite IR-120 (H^+) (ii) H_2, Pd black, Pr^{i}OH; (iii) EDCI, HOBt, DIPEA, DCM, 0 °C to RT, 16 h.



Scheme 9 *Reagents and conditions*: (i) TFA-$CHCl_3$ (1 : 1), Pr^{i}OH, water.

shift distribution observed in the ^{1}H NMR spectra. Confirmation that the lowest-frequency ^{1}H NMR amide resonances were due to those amide protons exposed to the solvent was provided by $CDCl_3$–dimethyl sulfoxide (DMSO) solvent titrations (Fig. 3). For both the tetramer **5** and octamer **6** the *N*-terminal amide NH_B demonstrated the greatest sensitivity by far to addition of DMSO, with shifts to high frequency arising from H-bonding interactions with the added solvent. In contrast, all other amide resonances showed markedly less alteration, indicating these to be relatively inaccessible to the solvent and involved in intramolecular hydrogen bonds. It was also apparent that for each of tetramer **5** and octamer **6**, NH_B was observed as a doublet of doublets (dd), compared with the remaining NH signals in the oligomer which were all apparent triplets (a-t).

Very similar NMR spectra were obtained for the cyclohexylidene-protected tetramer **5** and the enantiomeric isopropylidene-protected tetramer **36**. For tetramer **5** in $CDCl_3$, assignment of NMR signals was achieved with 2D NMR experiments, including COSY, TOCSY, HMQC and HMBC experiments. From the analysis of rotating-frame NOE data, and through comparison with tetramer **36** for which extensive NOE studies (ROESY and Tr-ROESY[24]) were conducted previously, a repeating 'β-turn' type structure is again suggested. Such a secondary structure also resembles that previously reported for the per-acetylated tetramer **35**.[5,25] Significant NOE interactions were observed from NH_i to $H2_{i-1}$ and from NH_i to $H6_{i-1}$ (stereo-specifically) for NH_C and NH_D in both tetramer **36** and tetramer **5**. Such NOE enhancements suggest H-bond interactions between NH_i and CO_{i-2} as shown in Fig. 4 for **5**.

This suggests that isopropylidene rather than cyclohexylidene moieties (as different ketal protecting groups) had very little effect on the gross conformation in solution.[26] This is consistent with the conformation described, as the secondary hydroxy-protecting groups would lie on the outside and away

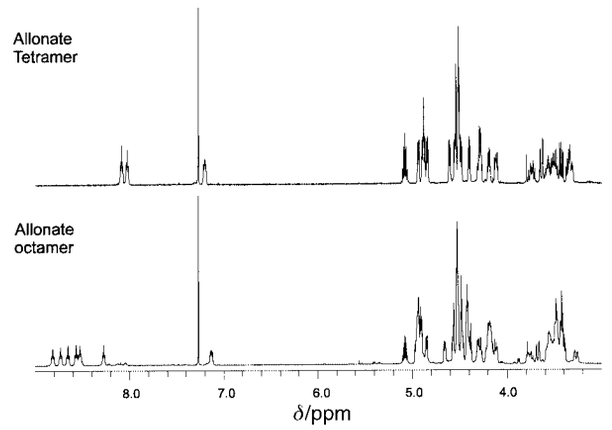
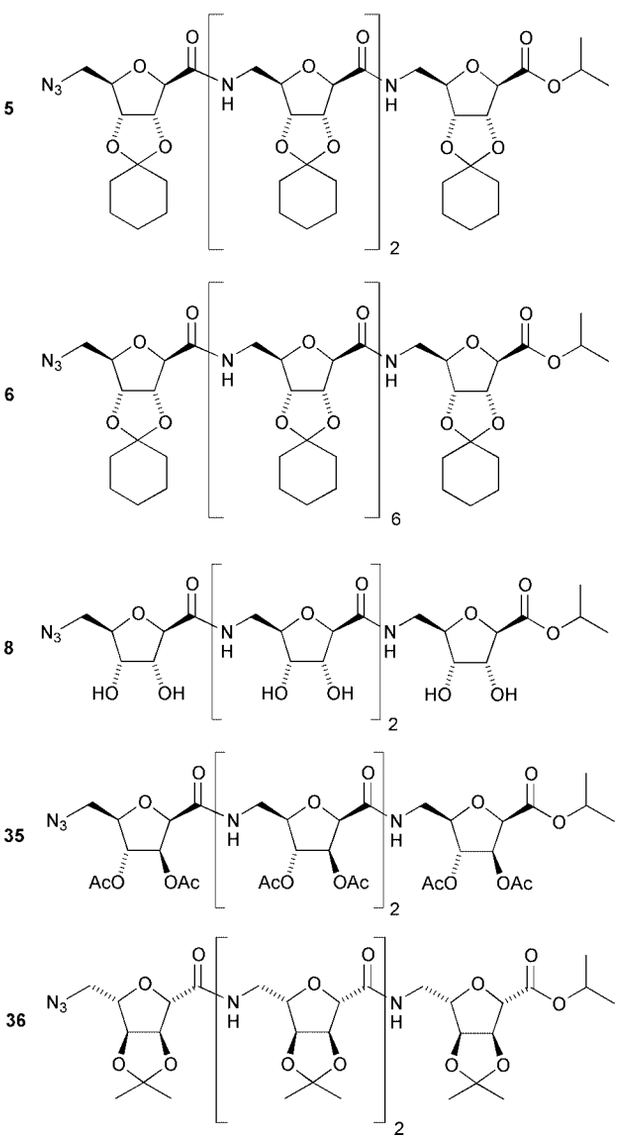


Fig. 1 ^{1}H NMR spectra of allonate tetramer **5** and allonate octamer **6** ($CDCl_3$; 298 K).



from the hydrogen bonds of the turn structure. Interestingly, a similar repeating structure to this, referred to as a 'β-bend ribbon spiral', has been observed crystallographically for oligomeric peptides of alternating L-proline and α-amino-isobutyric acid units,[27,28] and in solution for a fungal peptide also containing this dipeptide motif.[29] These peptides contain a repeating 10-membered hydrogen-bonded ring structure highly reminiscent of that proposed by us for tetramers **35**, **36** and **5**.

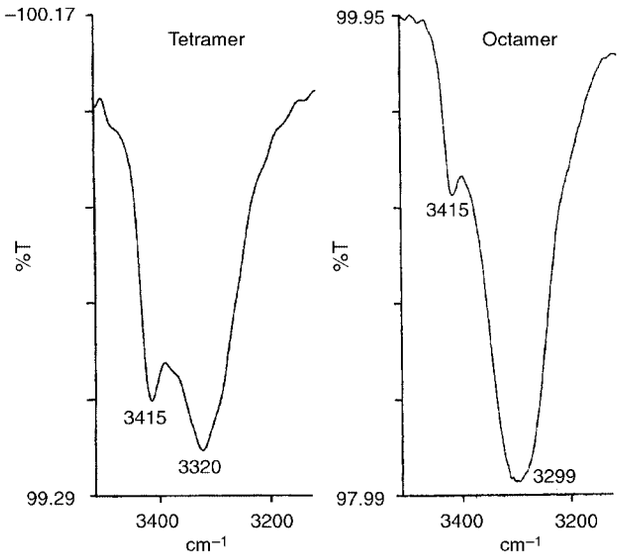


Fig. 2 IR spectra of tetramer **5** and octamer **6** showing the amide N–H stretch region (2 mM in $CHCl_3$).

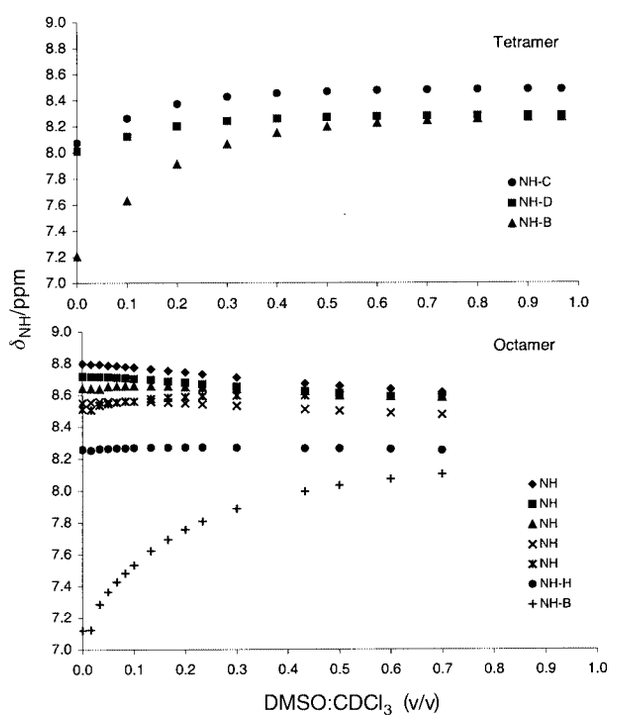


Fig. 3 Solvent titration plots (DMSO additions to initial 7 mM $CDCl_3$ solutions) for the amide NH protons of tetramer **5** and octamer **6**.

A similar secondary structure is suggested for the octamer **6** based on the similarity of the NMR spectra. The ^{1}H chemical shifts (as identified in the 2D TOCSY experiment) suggested that the central sugar residues of the repeating-turn structure experience similar environments and hence similar chemical shifts. Signals from rings A, B and H tended to be separated from the same protons in these central rings, which were observed to overlap. Despite this, distinct resonances were observed for each of NH_B through to NH_H. Again NH_B (δ 7.12) was observed at lowest frequency, typical of no hydrogen-bonding interactions, whilst the H-bonded *C*-terminal NH_H (δ 8.26) was observed at lower frequency than NH_{C-G} (which could not be assigned sequentially due to sugar-resonance overlap). This observation is consistent with a structure in which the C=O of residue G (which forms the amide bond with NH_H) is not able to participate in H-bonding, meaning the NH_H amide proton is therefore less deshielded than those of residues

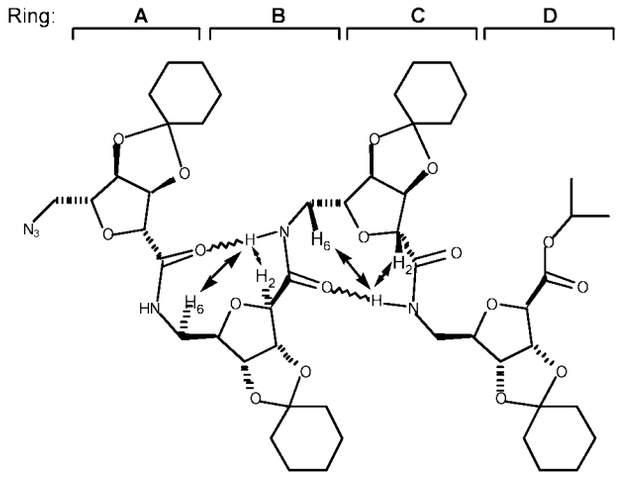


Fig. 4 The H-bonding pattern suggested for tetramer **5** from the observed strong NOEs.

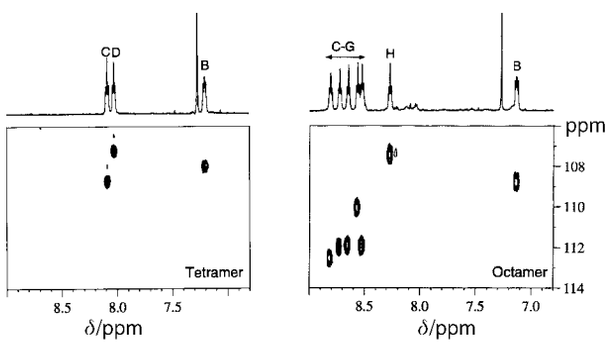


Fig. 5 The ^{1}H–^{15}N HSQC spectra of the tetramer **5** and octamer **6** ($CDCl_3$; 298 K).

C–G in which both the NH and C=O of each amide bond do participate.[21] A similar, although less marked, pattern was also observed for NH_D in tetramer **5** which resonated at lower frequency than NH_C. These trends are also reflected by the ^{15}N amide chemical shifts observed in the ^{1}H–^{15}N HSQC spectra of tetramer **5** and octamer **6** (Fig. 5). In both cases, the lowest-frequency ^{15}N resonance observed corresponded to the *C*-terminal residue in which the NH is involved in hydrogen bonding but the carbonyl of the amide bond is not [NH_D (δ 107.2) and NH_H (δ 107.4) respectively]. The next-lowest-frequency ^{15}N resonance at δ 108.0 for tetramer **5** and δ 108.8 for octamer **6** both corresponded to NH_B signals, associated with involvement of C=O in hydrogen bonding, but no participation of NH_B in further hydrogen-bonding interactions. Simultaneous involvement of both the NH and the C=O in intramolecular hydrogen bonding resulted in higher-frequency resonances for ^{1}H and ^{15}N signals. Furthermore, the greater ^{1}H and ^{15}N shifts observed for the central residues of the octamer **6** relative to the shifts of the tetramer **5** amide groups suggest a greater polarisation of the amide bonds, and a net strengthening of H-bonds in the longer structure. The lower-frequency hydrogen bonded amide NH IR stretch of the octamer **6** relative to the tetramer **5** (3299 *vs.* 3320 cm^{-1}) is also consistent with this.

This simple rationalisation of the observed patterns of ^{1}H and ^{15}N resonance shifts on the basis of amide NH and/or CO involvement argues for the amide protons intramolecularly hydrogen bonding to the backbone carbonyl moieties as in Fig. 4 rather than with side-chain or backbone ether oxygens. Such main-chain-to-side-chain interactions have been observed crystallographically in conformationally restricted peptides and shown to *destabilise* helix formation.[30] Whilst such interactions may provide a competitive destabilising influence on otherwise well defined conformations, it is unlikely that these would be sufficient to produce stable conformations in the absence of more conventional peptide N–H-to-C=O hydrogen bonds. Previous NOE and molecular-modelling studies on tetramer **35**[5] have shown carbonyl H-bonds alone to satisfy the NOE constraints, so although the formation of NH–O_{ether} interactions (and possibly simultaneous HN interactions with the THF ring oxygen within the 'β-turn' in particular) cannot be ruled out completely, these do not appear to be responsible for the observed secondary structure on tetramer **5**, octamer **6** and related oligomers.

In the case of the deprotected tetramer **8**, preliminary NMR studies were also conducted into its solution conformation. NMR spectra in d_5-pyridine enabled a comparison between the protected and deprotected tetramers **5** and **8**, respectively. In both cases, amide and sugar-ring proton dispersion was again observed, despite the repeating monomer units. For protected tetramer **5**, amide protons were observed at δ 8.96, 9.02, and 9.24, whereas for the deprotected tetramer **8**, NH signals were observed at δ 8.68, 9.06, and 9.26. It is interesting to note that for protected tetramer **5** in d_5-pyridine, the pattern of amide protons had changed, with two at lower-frequency and one slightly more separated and at higher frequency. In this case all NH signals were observed as apparent triplets. By comparison, the deprotected tetramer **8** in d_5-pyridine again showed the same pattern as for protected tetramer **5** and octamer **6** in $CDCl_3$, with the low-frequency NH (δ 8.68) observed as a doublet of doublets, and the higher-frequency signals all observed as apparent triplets.

The spectrum of deprotected tetramer **8** was additionally recorded in CD_3OH to assess whether secondary structure was observed in this more polar protic solvent. Again, sufficient dispersion enabled assignment of all sugar-ring protons and the amide protons were observed at δ 8.07 (NH_B), 8.36 (NH_D) and 8.53 (NH_C) in a similarly disperse pattern to that observed for protected tetramer **5** in $CDCl_3$. Again, the lower-frequency NH was observed as a doublet of doublets compared with the others which were apparent triplets. The ^{1}H and ^{13}C NMR were assigned with the aid of DQFCOSY, TOCSY, HSQC and HMBC 2D NMR experiments. The CD_3OH NOESY experiment for deprotected **8** exhibited for NH_B, NH_C and NH_D, cross-peaks between NH_i and $H2_{i-1}$, NH_i and $H3_{i-1}$, NH_i and $H4_{i-1}$ and between NH_i and $H6_{i-1}$ (overlapping signals prevent this last observation for NH_D to H-6_C). As for protected **5** in $CDCl_3$, this evidence suggests a 'β-turn'-type solution structure. Any difference to **5** could be attributed to the differing conformation in this solvent or be due to the lack of extra constraint without the cyclohexylidene groups. It is also likely that methanol could disrupt the stable conformer through solvent–solute H-bond interactions. Nevertheless a repeating pattern of NOEs is observed from NH_i to protons in the adjacent residue and good dispersion of protons resonances is seen. Further evidence is needed to establish whether a repeating structure along the molecule **8** remains in CD_3OH.

A ^{1}H NMR spectrum of deprotected **8** was additionally recorded in a solvent system consisting of 10% D_2O in H_2O. In this aqueous system, three distinct NH signals were observed at δ 8.18, 8.25 and 8.40, again suggesting that the structure exhibits a conformational preference in this environment, although further studies are again required to fully assess this preference.

Summary

Homooligomers of D-*allo*-configured amino acid monomer units are readily synthesised and purified, with the ketal protecting group providing manageable oligomeric materials. Preliminary evidence indicates that the tetramer and octamer, as short oligopeptides, exhibit secondary structure in solution, consistent with a 'β-turn'-like structure. Deprotection can afford materials that are soluble in aqueous environments. Evi-

dence is accumulating that different diastereomeric 5-(aminomethyl)-THF-carboxylate building blocks may have structural features that are predisposed to induce different types – or a lack – of secondary structures leading to a family of foldamers. Further NMR studies and CD spectra should provide further evidence of defined structures and help establish tetrahydrofuran amino acids as peptidomimetic building blocks with predictable predisposition to the formation of defined secondary structures.

Experimental

^{1}H NMR (δ_H) spectra were recorded on a Bruker DPX 400 spectrometer (at 400 MHz), Bruker DPX 200 or Varian Gemini 200 (200 MHz), Bruker AMX 500 or AM 500 (500 MHz) spectrometer at ambient probe temperatures (≈298 K). Coupling constants (J) were measured in Hz and are averaged. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Bruker DPX 200 (at 50 MHz), on a Bruker DPX 400 spectrometer (at 100 MHz) or a Bruker AMX 500 or AM500 (125 MHz) spectrometer; multiplicities were assigned using a DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as internal standard, except for the $CDCl_3$–DMSO solvent titrations which were referenced to internal $SiMe_4$ (TMS) which was assumed to be invariant to solvent changes. TOCSY spectra were collected using the MLEV-17 mixing sequence with mixing times of up to 100 ms. HSQC spectra were acquired with gradient selection.[31] For ^{1}H–^{15}N HSQC spectra, ^{15}N was referenced against external liquid NH_3. ROESY spectra were acquired with either a continuous-wave spin-lock or with the $180_x - 180_{-x}$ composite spin-lock sequence to suppress TOCSY transfers (Tr-ROESY). Mixing times were 300 ms.[24] IR spectra were recorded on a Perkin-Elmer 1750 IR FT spectrophotometer. Solution IR spectra were recorded in a 1 mm cell at a concentration of 2 mM in $CHCl_3$. Mass spectra were recorded on VG Micromass 20–250, ZAB 1F, Micromass Platform 1 or Trio-1 GCMS (DB-5 column) spectrometers using chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray techniques (ES) as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. $[\alpha]_D$-Values are given in 10^{-1} deg cm^2 g^{-1}. Concentrations are given in g 100 ml^{-1}. Mps were recorded on a Kofler block and are uncorrected. Microanalyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford. TLC was carried out on plastic or aluminium sheets coated with $60F_{254}$ silica or on glass plates coated with silica blend 41. Plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Hydrogenations were conducted under an atmosphere of hydrogen gas maintained by an inflated balloon. Solvents and commercially available reagents were dried and purified before use according to standard procedures. A solution of KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 ml) was used as a pH 7 buffer solution. The cyclohexylidene δ-lactone **12** was prepared as previously described.[14,16]

3,4-*O*-Cyclohexylidene-6-*O*-(*p*-tolylsulfonyl)-D-altrono-1,5-lactone 13

Powdered dry 3 Å sieves (0.3 g) and the protected lactone **12** (0.30 g, 1.16 mmol) were stirred in dry pyridine (3 mL) under a N_2 atmosphere for 30 min. The reaction mixture was then cooled to 0 °C and toluene-*p*-sulfonyl chloride (*p*-TsCl) (0.289 g, 1.5 mmol) was added. Stirring was continued overnight at room temperature, when TLC analysis (ethyl acetate–hexane 1 : 1) indicated a major product (R_f 0.4) and a minor component (R_f 0.6) and little residual starting material (R_f 0.2). Water (1 mL) was added and the pyridine was removed *in vacuo* by co-evaporation with toluene. DCM (80 mL) was added and the mixture was washed successively with saturated aq. $CuSO_4$ (50 mL), water (30 mL) and saturated aq. sodium bicarbonate (30 mL). The organic solution was then dried ($MgSO_4$), and concentrated by rotary evaporation. Flash chromatography (ethyl acetate–hexane 1 : 2) gave the ditosyl compound **14** (0.049 g, 7%) as a foam, followed by the monotosylester **13** (0.29 g, 61%), mp 45–47 °C; $[\alpha]_D^{24}$ +75.4 (*c* 1.14 in $CHCl_3$) [HRMS *m*/*z* (CI+): Found: 430.1531 (M + NH_4^+). $C_{19}H_{28}NO_8S$ requires *m*/*z*, 430.1536]; ν_{max} (thin film) 3469 (OH), 1769 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.40–1.78 (10H, m, cyclohexylidene), 2.50 (3H, s, CH_3Ar), 4.23–4.36 (4H, m, H-3, -4, -5, -6), 4.43 (1H, d, *J* 6.5, H-2), 4.48 (1H, d, *J* 10.4, H′-6), 7.42 (2H, d, *J* 8.2, ArH), 7.87 (2H, d, *J* 8.2, ArH); δ_C ($CDCl_3$; 126 MHz) 22.1 (q, CH_3Ar), 23.8, 24.2, 25.3, 34.4, 37.1 (5 × t, cyclohexylidene), 67.6 (t, C-6), 70.3, 71.2, 75.9, 77.0 (4 × d, C-2, -3, -4, -5), 114.2 (s, O–C–O), 128.6 (d, Ar CH), 130.5 (d, Ar CH), 132.7 (s, Ar C), 145.8 (s, Ar C), 171.9 (s, C-1); *m*/*z* (APCI+) 413 (M + H$^+$, 100%).

Continued chromatography with ethyl acetate–hexane 1 : 1 gave residual starting material **12** (0.043 g, 14% recovery).

2,6-Anhydro-3,4-*O*-cyclohexylidene-D-altrono-1,5-lactone 16 and 6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-altrono-1,5-lactone 15

The monotosyl derivative **13** (0.050 g, 0.12 mmol) was dissolved in dry DMF (1 mL), and sodium azide (0.017 g, 0.25 mmol) was added. The mixture was stirred at 70 °C for 16 h followed by 1 h at 90 °C. TLC analysis (ethyl acetate–hexane 1 : 1) showed two non-UV-active spots (R_f 0.5 and 0.4) while the starting material was UV-active (R_f 0.4). Water (5 drops) was added and the DMF was removed *in vacuo*. Brine (10 mL) was added to the residue, which was then extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (ethyl acetate–hexane 1 : 2) enabled separation of the two products, giving the bicyclic lactone **16**[16] (0.010 g, 35%) and the azide **15**[15] (0.002 g, 6%), both with physical properties identical with those reported previously.[15,16]

3,4-*O*-Cyclohexylidene-6-*O*-(*p*-toluenesulfonyl)-2-*O*-trifluoromethanesulfonyl-D-altrono-1,5-lactone 17

Dry pyridine (0.067 mL, 0.066 g, 0.83 mmol) was added to a solution of the tosyl ester **13** (0.149 g, 0.36 mmol) dissolved in dry DCM (2 mL). Upon cooling of the mixture to −40 °C, trifluoromethanesulfonic anhydride (0.079 mL, 0.133 g, 0.47 mmol) was added dropwise *via* syringe. Stirring was continued for 20 min between −40 and −20 °C. TLC analysis (ethyl acetate–hexane 1 : 1) revealed a single product (R_f 0.7) and no residual starting material (R_f 0.4). The reaction mixture was diluted with DCM, washed with water with drops 2 M HCl added (total aqueous volume 10 mL) and then with pH 7 buffer, and then dried ($MgSO_4$) and concentrated. Flash chromatography (ethyl acetate–hexane 1 : 4) gave the triflate **17** (0.168 g, 85%), an unstable foam which was used directly in the next reaction; ν_{max} (thin film) 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.38–1.73 (10H, m, cyclohexylidene), 2.46 (3H, s, CH_3Ar), 4.26–4.36 (2H, m), 4.39–4.44 (2H, m), 4.55 (1H, a-t, *J* 7.6, H-3), 5.19 (1H, d, *J* 7.6, H-2), 7.38 (2H, d, *J* 8.2, ArH), 7.81 (2H, d, *J* 8.2, ArH); δ_C ($CDCl_3$; 100.6 MHz) 21.6 (q, CH_3Ar), 23.3, 23.7, 24.7, 34.0, 36.5 (5 × t, cyclohexylidene), 66.7 (t, C-6), 70.0, 73.7, 75.7, 81.3 (4 × d, C-2, -3, -4, -5), 114.9 (s, O–C–O), 118.3 [q, J(^{13}C–^{19}F) 320, CF_3], 128.1 (d, Ar CH), 130.0 (d, Ar CH), 132.0 (s, Ar C), 145.6 (s, Ar C), 162.9 (s, C-1); *m*/*z* (APCI+) 567 (M + Na$^+$, 20%), 545 (M + H$^+$, 12), 411 (20), 297 (85), 295 (80), 217 (100), 122 (85).

3,4-*O*-Cyclohexylidene-2,6-bis-*O*-(*p*-tolylsulfonyl)-D-altrono-1,5-lactone 14

Powdered dry 3 Å sieves (1.0 g) and the lactone **12** (2.74 g,

10.6 mmol) were stirred in dry pyridine (50 mL) under a N_2 atmosphere for 30 min. The reaction mixture was then cooled to 0 °C and toluene-*p*-sulfonic anhydride (8.09 g, 24.8 mmol) was added. Stirring was continued overnight at room temperature. TLC analysis (ethyl acetate–hexane 1:2) indicated a major product (R_f 0.3) and a minor component (R_f 0.2) and no residual starting material (R_f 0.08). This mixture was filtered through Celite and then concentrated *in vacuo*. The residue obtained was dissolved in DCM (150 mL) and washed with buffer (80 mL). The buffer wash was further extracted with DCM (3 × 50 mL) and the combined DCM phases were dried over $MgSO_4$ and concentrated. Flash chromatography (ethyl acetate–hexane 1:2) gave *3,4-O-cyclohexylidene-2,6-bis-O-(p-tolylsulfonyl)-D-altrono-1,5-lactone* **14** (5.34 g, 89%) as a foaming white solid, mp 63–64 °C [HRMS *m*/*z* (CI+) Found: 567.1350 ($M + H^+$). $C_{26}H_{31}O_{10}S_2$ requires *m*/*z*, 567.1359] (Found: C, 55.23; H, 5.48. $C_{26}H_{30}O_{10}S_2$ requires C, 55.11; H, 5.34%); $[\alpha]_D^{24}$ +13.5 (*c* 1.35 in $CHCl_3$); ν_{max} (thin film) 1786 (C=O, lactone) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.30–1.70 (10H, m, cyclohexylidene), 2.45 (3H, s, CH_3Ar), 2.46 (3H, s, CH_3Ar), 4.22–4.31 and 4.35–4.40 (3H and 2H, m, H-3, -4, -5, H_2-6), 5.15 (1H, d, *J* 7.2, H-2), 7.36 (4H, m, ArH), 7.81 (2H, d, *J* 8.2, ArH), 7.87 (2H, d, *J* 8.2 Hz, ArH); δ_C ($CDCl_3$; 100.6 MHz) 21.7, 21.7 (2 × q, 2 × CH_3Ar), 23.3, 23.7, 24.7, 34.0, 36.5 (5 × t, cyclohexylidene, 5 × CH_2), 66.9 (t, C-6), 70.0, 74.5, 75.3, 76.3 (4 × d, C-2, -3, -4, -5), 114.1 (s, O–C–O), 128.1, 128.3, 129.7, 130.0 (4 × d, 4 × Ar CH), 132.1, 133.2 (2 × s, 2 × Ar C), 145.3, 145.4 (2 × s, 2 × Ar C), 164.2 (s, O–C=O); *m*/*z* (APCI+) 567 ($M + H^+$, 100%).

Methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-6-*O*-(*p*-tolylsulfonyl)-D-allonate 19 and methyl 2,5-anhydro-3,4-*O*-cyclohexylidene-6-*O*-(*p*-tolylsulfonyl)-D-altronate 20

Method 1 (from the triflate 17). Potassium carbonate (0.030 g, 0.22 mmol) was added to a stirred solution of the triflate **17** (0.119 g, 0.22 mmol) in MeOH (4 mL). After 1 h, TLC analysis (ethyl acetate–hexane 1:1) indicated complete conversion of the starting material (R_f 0.73) to a major product (R_f 0.65). The reaction mixture was concentrated *in vacuo*, the residue was re-dissolved in DCM, and the solution was filtered through Celite, which was then washed with DCM. Concentration *in vacuo* gave a residue, which was purified by flash chromatography (ethyl acetate–hexane 1:4) to yield the *allonate* **19** (0.062 g, 67%) as a colourless oil, $[\alpha]_D^{24}$ −11.5 (*c* 1.13 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 426.1344 (M^+). $C_{20}H_{26}O_8S$ requires *M*, 426.1348] (Found: C, 56.24; H, 6.49. $C_{20}H_{26}O_8S$ requires C, 56.32; H, 6.14%); ν_{max} (thin film) 1752 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.30–1.48 (2H, m, cyclohexylidene), 1.50–1.69 (6H, m, cyclohexylidene), 1.70–1.78 (2H, m, cyclohexylidene), 2.46 (3H, s, CH_3Ar), 3.77 (3H, s, OCH_3), 4.09 (1H, dd, *J* 10.5, 5.0, H-6), 4.14 (1H, dd, *J* 10.5, 4.2, H′-6), 4.37 (1H, m, H-5), 4.54 (1H, d, *J* 2.7, H-2), 4.63 (1H, dd, *J* 6.1, 1.9, H-4), 4.95 (1H, dd, *J* 6.1, 2.7, H-3), 7.36 (2H, d, *J* 8.3, ArH), 7.80 (2H, d, *J* 8.3, ArH); δ_C ($CDCl_3$; 100.6 MHz) 21.6 (q, CH_3Ar), 23.6, 23.9, 24.9, 34.5, 36.6 (5 × t, CH_2, cyclohexylidene), 52.5 (q, CH_3O), 69.4 (t, C-6), 81.7 (d, C-4), 83.2, 83.4 (2 × d, C-3, -5), 84.5 (d, C-2), 114.7 (s, O–C–O), 128.0 (d, Ar CH), 129.9 (d, Ar CH), 132.3 (s, Ar C), 145.1 (s, Ar C), 170.6 (s, O–C=O); *m*/*z* (APCI+) 427 ($M + H^+$, 100%), 449 ($M + Na^+$, 50), 255 (50).

Method 2 (from the ditosylate compound 14). Potassium carbonate (1.30 g, 9.4 mmol) was added to a stirred solution of the ditosyl compound **14** (5.34 g, 9.4 mmol) in MeOH (150 mL). The solution immediately turned from colourless to orange and stirring was continued for 1 h. TLC analysis (ethyl acetate–hexane 1:4) then indicated complete conversion of the starting material (R_f 0.1) to a major product (R_f 0.15) and a minor product at slightly lower R_f (0.1). The reaction mixture was concentrated *in vacuo*, the residue was re-dissolved in DCM, and the solution was filtered through Celite, which was afterwards washed with DCM. Concentration of the filtrate gave a dark red crude product, which was purified by flash chromatography (ethyl acetate–hexane 1:4) to yield the allonate **19** (2.25 g, 56%) (see data above).

Further elution afforded the altronate **20** (0.22 g, 6%); $[\alpha]_D^{24}$ −7.3 (*c* 2.55 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 444.1697 ($M + NH_4^+$). $C_{20}H_{30}NO_8S$ requires *m*/*z*, 444.1692]; ν_{max} (thin film) 1765 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.29–1.43 (2H, m, cyclohexylidene), 1.45–1.60 (6H, m, cyclohexylidene), 1.61–1.73 (2H, m, cyclohexylidene), 2.45 (3H, s, CH_3Ar), 3.78 (3H, s, OCH_3), 4.09 (1H, dd, *J* 10.7, 3.1, H-6), 4.14 (1H, dd, *J* 10.7, 3.0, H′-6), 4.45 (1H, m, H-5), 4.62 (1H, d, *J* 5.1, H-2), 4.76 (1H, dd, *J* 6.0, 1.3, H-4), 5.03 (1H, a-t, H-3), 7.36 (2H, d, *J* 8.3, ArH), 7.77 (2H, d, *J* 8.3, ArH); δ_C ($CDCl_3$; 100.6 MHz) 21.7 (q, CH_3Ar), 23.7, 23.8, 24.9, 34.5, 35.7 (5 × t, CH_2, cyclohexylidene), 52.1 (q, OCH_3), 70.6 (t, C-6), 81.4 (d, C-3 or -4), 81.5 (d, C-4 or -3), 82.1 (d, C-2), 82.4 (d, C-5), 114.5 (s, O–C–O), 127.9 (d, Ar CH), 130.1 (d, Ar CH), 132.0 (s, Ar C), 145.4 (s, Ar C), 168.3 (s, O–C=O); *m*/*z* (APCI+) 427 ($M + H^+$, 100%).

Methyl 2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate 18

The THF tosyl ester **19** (2.25 g, 5.28 mmol) was dissolved in DMF (45 mL), sodium azide (0.721 g, 11.1 mmol) was added in one portion, and the mixture was stirred at 85 °C for 2 h. TLC (ethyl acetate–hexane 1:1) indicated complete conversion of the starting material (R_f 0.6) to a single product (R_f 0.7). Water (10 drops) was added and the mixture was allowed to cool and was concentrated *in vacuo* (co-evaporation with toluene). Buffer (pH 7; 50 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (ethyl acetate–hexane 1:5) afforded the azide **18** (1.44 g, 92%) as a colourless oil, $[\alpha]_D^{24}$ +23.9 (*c* 1.15 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 297.1330 (M^+). $C_{13}H_{19}N_3O_5$ requires *M*, 297.1325]; ν_{max} (thin film) 2096 (N_3), 1747 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.40–1.52 (2H, m, cyclohexylidene), 1.55–1.75 (6H, m, cyclohexylidene), 1.76–1.85 (2H, m, cyclohexylidene), 3.48 (1H, dd, *J* 12.9, 4.6, H-6), 3.59 (1H, dd, *J* 12.9, 5.9, H′-6), 3.85 (3H, s, OCH_3), 4.36 (1H, m, H-5), 4.62–4.64 (1H, m, H-4), 4.63 (1H, d, *J* 2.8, H-2), 4.97 (1H, dd, *J* 6.2, 2.9, H-3); δ_C ($CDCl_3$; 126 MHz) 23.6, 23.9, 24.9, 34.7, 36.8 (5 × t, CH_2, cyclohexylidene), 52.5 (q, OCH_3), 52.5 (t, C-6), 82.1 (d, C-2 or -4), 83.3 (d, C-3), 84.0 (d, C-4 or -2), 84.9 (d, C-5), 115.0 (s, O–C–O), 170.8 (s, O–C=O); *m*/*z* (APCI+) 270 ($M + H^+ - N_2$, 60%), 154 (100).

6-Amino-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonolactam 22

A solution of the azidomethyl ester **18** (0.039 g, 0.13 mmol) in methanol (0.5 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (3 mg, 10%-wt). After 1 h, TLC (ethyl acetate–hexane 1:5) indicated an absence of starting material (R_f 0.3) and a major product (R_f 0.0). Further analysis by TLC (ethyl acetate–hexane 5:1) revealed a product spot (R_f 0.2). Filtration through Celite and flash chromatography purification (ethyl acetate–hexane 3:1) gave the bicyclic lactam **22** as a white solid (0.020 g, 64%), mp 213–215 °C; $[\alpha]_D^{24}$ +23.3 (*c* 0.48 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 240.1235 ($M + H^+$). $C_{12}H_{18}NO_4$ requires *m*/*z*, 240.1236]; ν_{max} (KBr disc). 3435, 3224 (NH), 1696 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.36–1.45 (2H, m, cyclohexylidene), 1.52–1.68 (6H, m, cyclohexylidene), 1.72–1.79 (2H, m, cyclohexylidene), 3.12 (1H, dd, *J* 11.9, 2.5, H-6), 3.66 (1H, dd, *J* 11.9, 4.9, H′-6), 4.43–4.47 (2H, m, H-2, -5), 4.71 (1H, d, *J* 5.8, H-3 or -4), 4.82 (1H, d, *J* 5.8, H-4 or -3), 6.33 (1H, br s, NH); δ_C ($CDCl_3$; 100.6 MHz) 23.6, 23.9, 25.0, 34.3, 35.6 (5 × t, CH_2, cyclohexylidene), 43.4 (t, C-6), 77.7, 81.9, 83.1, 83.8 (4 × d, C-2, -3, -4, -5),

114.0 (s, O–C–O), 168.7 (s, NH–C=O); *m/z* (APCI+) 240 (M + H^+, 100%).

Isopropyl 2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate 24 and isopropyl 2,5-anhydro-6-azido-6-deoxy-D-allonate 23

The methyl ester **18** (0.120 g, 0.404 mmol) was stirred in a 5% v/v solution of HCl in propan-2-ol (78 μL of acetyl chloride was added to 1.5 mL of propan-2-ol), and stirred at 80 °C for 3 h. TLC (ethyl acetate–hexane 1:5) showed a new product (R_f 0.4) and very little residual starting material (R_f 0.3) with a small amount of base-line product (R_f 0.0). Solid sodium bicarbonate (100 mg, excess) was added, and the reaction mixture was stirred for 20 min and then filtered through Celite. Concentration *in vacuo* and purification of the residue by flash chromatography (ethyl acetate–hexane 1:10) afforded *the oily isopropyl ester* **24** (0.109 g, 83%) as the major product, $[\alpha]_D^{24}$ +16.0 (*c* 0.23 in $CHCl_3$) [HRMS *m/z* (CI+) Found: 298.1663 (M + H^+ − N_2). $C_{15}H_{24}NO_5$ requires *m/z*, 298.1654] (Found: C, 55.70; H, 7.04; N, 12.47. $C_{15}H_{23}N_3O_5$ requires C, 55.37; H, 7.13; N, 12.91%); ν_{max} (thin film) 2103 (N_3), 1745 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.30 [6H, a-d, *J* 6.3, CH(CH_3)$_2$], 1.32–1.48, (2H, m, cyclohexylidene), 1.53–1.71 (6H, m, cyclohexylidene), 1.75–1.80 (2H, m, cyclohexylidene), 3.39 (1H, dd, *J* 12.9, 4.8, H-6), 3.56 (1H, dd, *J* 12.9, 6.3, H′-6), 4.32 (1H, m, H-5), 4.56 (1H, d, *J* 2.6, H-2), 4.58 (1H, dd, *J* 6.2, 2.6, H-4), 4.90 (1H, dd, *J* 6.2, 2.6, H-3), 5.10 [1H, sept, *J* 6.3 Hz, C*H*(CH$_3$)$_2$]; δ_C ($CDCl_3$; 100.6 MHz) 21.69, 21.71 [2 × q, CH(*C*H$_3$)$_2$], 23.6, 23.9, 24.9, 34.8, 36.7 (5 × t, CH_2, cyclohexylidene), 52.5 (t, C-6), 69.4 [d, O*C*H(CH$_3$)$_2$], 82.2, 83.5, 84.4, 85.2 (4 × d, C-2, -3, -4, -5), 114.8 (O–C–O), 170.1 (O–C=O); *m/z* (APCI+): 298 (M + H^+ − N_2).

Also eluted was with the isopropyl diol **23** (0.011 g, 11%) isolated as the minor product, mp 78–79 °C; $[\alpha]_D^{24}$ +72.4 (*c* 0.45 in MeOH) [HRMS *m/z* (CI+) Found: 246.1086 (M + H^+). $C_9H_{16}N_3O_5$ requires *m/z*, 246.1090] (Found: C, 44.14; H, 6.32; N, 16.32. $C_9H_{15}N_3O_5$ requires: C, 44.08; H, 6.17; N, 17.13%); ν_{max} (thin film) 3415 (OH), 2099 (N_3), 1731 (C=O, ester) cm^{-1}; δ_H (CD_3OD; 500 MHz) 1.26 (3H, d, *J* 6.3, CHCH_3), 1.27 (3H, d, *J* 6.3, CHCH_3), 3.43 (1H, dd, *J* 13.2, 6.1, H-6), 3.49 (1H, dd, *J* 13.2, 3.2, H′-6), 3.93 (1H, dd, *J* 6.9, 5.0, H-4), 4.01 (1H, m, H-5), 4.16 (1H, dd, *J* 4.9, 3.1, H-3), 4.31 (1H, d, *J* 3.0, H-2), 5.04 [1H, sept, *J* 6.3, C*H*(CH$_3$)$_2$]; δ_C (CD_3OD; 126 MHz) 21.88, 21.92 [2 × q, CH(*C*H$_3$)$_2$], 53.7 (t, C-6), 70.3, 73.7, 75.7, 83.5, 84.3 [5 × d, C-2, -3, -4, -5, O*C*H(CH$_3$)$_2$], 172.0 (s, O–C=O); *m/z* (APCI−) 280 (M + Cl^-, 100%).

A small amount of the starting methyl ester **18** (0.008 g, 6%) was also recovered.

Proof of structure: conversion from cyclohexylidene to isopropylidene protecting groups

Methyl 2,5-anhydro-6-azido-6-deoxy-3,4-*O*-isopropylidene-D-allonate 26 from 18. The cyclohexylidene-protected methyl ester **18** (0.076 g, 0.26 mmol) was stirred in a mixture of trifluoroacetic acid and water (2:3; 8 mL) at room temperature. After 1 h, TLC (ethyl acetate–hexane 1:1) suggested complete conversion to a single product (R_f 0.1) (no starting material at R_f 0.6). The solvent was removed under reduced pressure and the residue was triturated with toluene; the crude residue together with (±)-camphorsulfonic acid (0.003 g, 1.25×10^{-5} mol) and 2,2-dimethoxypropane (0.03 g, 0.3 mmol) was dissolved in acetone (1 mL) and the solution was stirred at room temperature for 2 h. TLC (ethyl acetate–hexane 1:1) indicated a new product (R_f 0.5). Solid sodium bicarbonate was added and the mixture was stirred for a further 30 min and then filtered through a small pad of Celite, which was then washed with acetone. The filtrate was concentrated to give crude product (0.065 g, 100%) which was used directly in the following reaction. A portion of the crude mixture was purified by flash chromatography (ethyl acetate–hexane 1:5) to give the isopropylidene methyl ester **26**, $[\alpha]_D^{24}$ +28.0 (*c* 0.45 in $CHCl_3$) [HRMS *m/z* (CI+) Found: 258.1080 (M + H^+). $C_{10}H_{16}N_3O_5$ requires *m/z*, 258.1090]; ν_{max} (thin film) 2106 (N_3), 1755 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.36 (3H, s, CH_3C), 1.56 (3H, s, CH_3C), 3.45 (1H, dd, *J* 12.9, 4.7, H-6), 3.55 (1H, dd *J* 12.9, 5.7, H′-6), 3.81 (3H, s, CH_3O), 4.31 (1H, m, H-5), 4.58 (1H, d, *J* 3.2, H-2), 4.60 (1H, dd, *J* 6.4, 2.7, H-4), 4.94 (1H, dd, *J* 6.3, 3.2, H-3); δ_C ($CDCl_3$; 50 MHz) 25.2 (q, *C*H_3C), 27.0 (q, *C*H_3C), 52.5 (t, C-6), 52.6 (q, OCH_3), 82.4, 83.6, 83.8, 84.7 (4 × d, C-2, -3, -4, -5), 114.3 (s, O–C–O), 170.7 (s, O–C=O); *m/z* (APCI+) 230 (M + H^+ − N_2, 100%).

6-Amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-D-allonolactam 27. Methyl 2,5-anhydro-6-azido-6-deoxy-3,4-*O*-isopropylidene-D-allonate **26** (0.040 g, 0.16 mmol) was dissolved in MeOH (0.5 mL) under a nitrogen atmosphere. Pd black (4 mg, 10%-wt) was added and the reaction mixture was stirred under a hydrogen atmosphere. After 1 h, TLC (ethyl acetate–hexane 5:1) showed the absence of starting material and a new product (at R_f 0.08). Filtration through Celite, concentration, and flash chromatography purification (100% ethyl acetate) yielded the isopropylidene lactam **27** (0.021 g, 68%) as a white solid, mp 193–195 °C (lit.[11] L-enantiomer **28**, 192 °C); $[\alpha]_D^{24}$ +34.4 (*c* 0.43 in $CHCl_3$) {lit.,[11] L-enantiomer **28** $[\alpha]_D^{23}$ −39.2 (*c*, 0.75 in $CHCl_3$), $[\alpha]_D^{22}$ −25.7 (*c*, 0.75 in EtOH)} [HRMS *m/z* (CI+) Found: 200.0926 (M + H^+). $C_9H_{14}NO_4$ requires *m/z*, 200.0923]; ν_{max} (KBr disc) 3433, 3215 (NH), 1698 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.34 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.13 (1H, dd, *J* 11.9, 2.7, H-6), 3.67 (1H, dd, *J* 11.9, 4.9, H′-6), 4.44–4.47 (2H, m, H-2, -5), 4.72 (1H, d, *J* 5.8, H-3 or -4), 4.84 (1H, d, *J* 5.8, H-4 or H-3), 6.23 (1H, br s, NH); δ_C ($CDCl_3$; 100.6 MHz) 24.8, 26.0 [2 × q, C(*C*H$_3$)$_2$], 43.5 (t, C-6), 77.6, 81.9, 83.6, 84.2 (4 × d, C-2, -3, -4, -5), 113.3 (s, O–C–O), 168.6 (s, NH–C=O); *m/z* (APCI+) 200 (M + H^+, 100%). The ^1H and ^{13}C NMR spectra of **27** were therefore identical with those of the enantiomeric lactam **28**.[11]

Confirmation of structure of the altronate product 20

Methyl 2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-altronate 29. The minor methyl ester product **20** (0.181 g, 0.42 mmol) was dissolved in DMF (4 mL), sodium azide (0.058 g, 0.89 mmol) was added in one portion, and the mixture was stirred at 90 °C for 2 h. TLC (ethyl acetate–hexane 1:1) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.6). Water (10 drops) was added and the mixture was concentrated *in vacuo* (co-evaporation with toluene). Buffer (pH 7; 20 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried over magnesium sulfate and concentrated. Flash chromatography (ethyl acetate–hexane 1:4) afforded *the azide* **29** (0.088 g, 70%) as a colourless oil, $[\alpha]_D^{25}$ +22.1 (*c* 0.67 in $CHCl_3$) [HRMS *m/z* (CI+) Found: 298.1397 (M + H^+). $C_{13}H_{20}N_3O_5$ requires *m/z* 298.1403] (Found: C, 52.25; H, 6.84; N, 13.92. $C_{13}H_{19}N_3O_5$ requires C, 52.52; H, 6.44; N, 14.13%); ν_{max} (thin film) 2104 (N_3), 1763 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.29–1.43 (2H, m, cyclohexylidene), 1.45–1.62 (6H, m, cyclohexylidene), 1.63–1.72 (2H, m, cyclohexylidene), 3.47 (1H, dd, *J* 13.0, 4.2, H-6), 3.56 (1H, dd, *J* 13.0, 3.9, H′-6), 3.80 (3H, s, OCH_3), 4.46 (1H, m, H-5), 4.71 (1H, dd, *J* 6.2, 1.9, H-4), 4.77 (1H, d, *J* 5.3, H-2), 5.06 (1H, a-t, H-3); δ_C ($CDCl_3$; 100.6 MHz) 23.7, 23.9, 24.9, 34.7, 35.9 (5 × t, cyclohexylidene), 52.1 (q, OCH_3), 52.8 (t, C-6), 81.5, 81.6, 82.1, 83.5 (4 × d, C-2, -3, -4, -5), 114.8 (s, O–C–O), 168.7 (s, O–C=O); *m/z* (APCI+) 320 (M + Na^+, 5%), 298 (M + H^+, 10), 270 (M + H^+ − N_2, 30), 154 (100).

Methyl 2,5-anhydro-6-azido-6-deoxy-3,4-*O*-isopropylidene-D-altronate 30. The cyclohexylidene protecting group in **29** was exchanged for the isopropylidene ketal in **30**. The cyclohexylidene ketal **29** (0.073 g, 0.25 mmol) was stirred in a mixture of

trifluoroacetic acid and water (2 : 3; 8 mL) at room temperature. After 24 h, TLC (ethyl acetate–hexane 1 : 1) suggested complete conversion to a single product (R_f 0.1) (no starting material at R_f 0.6). The solvent was removed under reduced pressure, and the residue was co-evaporated with toluene; the crude diol intermediate (0.053 g, 0.25 mmol) was not isolated further and immediately treated with (±)-camphorsulfonic acid (0.003 g, 1.3 × 10–5 mol) and 2,2-dimethoxypropane (0.033 g, 0.3 mmol) dissolved in acetone (1 mL) and the solution was stirred at room temperature for 16 h. TLC (ethyl acetate–hexane 1 : 1) indicated a new product (R_f 0.5), but some remaining starting material (R_f 0.1). Solid sodium bicarbonate was added and the mixture was stirred for a further 30 min and then filtered through a small pad of Celite, with washing of the pad with acetone. The filtrate was concentrated, and purified by flash chromatography (ethyl acetate–hexane 1 : 5) to give the acetonide **30** (0.021 g, 31%) and recovered intermediate diol, methyl 2,5-anhydro-6-azido-6-deoxy-D-altronate. *Title product showed* [HRMS *m/z* (CI+) Found: 258.1097 (M + H$^+$). $C_{10}H_{16}N_3O_5$ requires *m/z*, 258.1090]; $[\alpha]_D^{24}$ +17.0 (*c* 1.06 in $CHCl_3$) {lit.,[17] $[\alpha]_D^{25}$ +17.9 (*c* 1.00 in $CHCl_3$)}; ν_{max} (thin film) 2101 (N_3), 1760 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$; 200 MHz) 1.33 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.46 (1H, dd, *J* 13.0, 4.2, H-6), 3.57 (1H, dd, *J* 13.0, 4.0, H′-6), 3.80 (3H, s, OCH_3), 4.46 (1H, m, H-5), 4.71 (1H, dd, *J* 6.2, 2.0, H-4), 4.79 (1H, d, *J* 5.3, H-2), 5.06 (1H, a-t, H-3); δ_C ($CDCl_3$; 100.6 MHz) 25.0, 26.2 [2 × q, $C(CH_3)_2$], 52.1 (q, OCH_3), 52.8 (t, C-6), 81.3 (d, C-2), 81.9 (d, C-3), 82.4 (d, C-4), 83.3 (d, C-5), 114.1 (s, O–C–O), 168.6 (s, O–C=O); *m/z* (APCI+) 258 (M + H$^+$, 5%), 230 (M + H$^+$ − N_2, 20), 154 (100). The ^{1}H and ^{13}C NMR spectra of our product **30** were therefore identical with those of an authentic sample.[17]

Protected and deprotected oligomers

The protected dimer, isopropyl 2,5-anhydro-6-(2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allononamido)-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate 4. Aq. sodium hydroxide (1 M; 0.36 mL, 0.36 mmol) was added to a stirred solution of methyl 2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate **18** (0.098 g, 0.33 mmol) in 1,4-dioxane (1.5 mL)–water (0.25 mL). The reaction mixture was stirred for 1 h at room temperature. TLC (ethyl acetate–hexane 1 : 5) indicated complete conversion of the starting material (R_f 0.3) to a major product (R_f 0.0). The solvent was removed *in vacuo* (co-evaporation with toluene), the residue was dissolved in water (1 mL), and the solution was stirred with Amberlite IR-120(H$^+$) resin for 10 min, during which time a white precipitate formed. DCM (2 mL) was added and this mixture was filtered directly through a sinter to remove the resin. Concentration *in vacuo* gave the crude carboxylic acid **21** (0.096 g) which was used directly in the coupling reaction.

A solution of the isopropyl azide **24** (0.109 g, 0.335 mmol) in propan-2-ol (0.5 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (11 mg, 10%-wt). After 30 min, TLC (ethyl acetate–hexane 1 : 5) indicated an absence of starting material (R_f 0.4) and the presence of a major product (R_f 0.0). Further analysis by TLC (ethyl acetate–hexane 5 : 1) revealed the presence of two products: the major component (R_f 0.1) was the amine **25** and the minor component (R_f 0.2) was the lactam **22**. To avoid further formation of the lactam **22** from the amine **25**, the reaction mixture was filtered through a small pad of tissue paper directly into the coupling-reaction vessel and the residue was washed with dichloromethane.

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.095 g, 0.50 mmol) was added to a stirred solution of the crude carboxylic acid **21** (0.33 mmol), followed by 1-hydroxybenzotriazole (0.068 g, 0.5 mmol) and diisopropylethylamine (87 μL, 0.065 g, 0.5 mmol) in dichloromethane (1 mL) at 0 °C. The reaction mixture was stirred for 30 min under a nitrogen atmosphere; then the filtered solution of the crude amine **25** (0.335 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight. TLC (ethyl acetate–hexane 5 : 1) indicated the formation of a major product (R_f 0.8) together with a small amount of residual lactam **22** (R_f 0.2). The reaction mixture was diluted with dichloromethane (30 mL) and washed with 0.5 M HCl (1 × 20 mL). The aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined dichloromethane phases were washed with pH 7 buffer, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (ethyl acetate–hexane 1 : 4) to yield *the dimer* **4** (0.138 g, 73%), $[\alpha]_D^{24}$ +25.4 (*c* 1.14 in $CHCl_3$) [HRMS *m/z* (CI+) Found: 565.2886 (M + H$^+$). $C_{27}H_{41}N_4O_9$ requires *m/z*, 565.2874] (Found: C, 57.22; H, 7.37; N, 8.89. $C_{27}H_{40}N_4O_9$ requires C, 57.43; H, 7.14; N, 9.92%); ν_{max} (thin film) 3407 (NH), 2106 (N_3), 1739 (C=O, ester), 1681 (C=O, amide I), 1530 (amide II) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 1.32 (3H, d, *J* 6.3, $CHCH_3$), 1.32 (3H, d, *J* 6.3, $CHCH_3$), 1.37–1.86 (20H, m, cyclohexylidene), 3.09 (1H, ddd, *J* 13.8, 9.2, 4.5, H-6$_B$), 3.59–3.67 (2H, m, CH_2N_3), 3.76 (1H, ddd, *J* 13.8, 7.6, 4.7, H′-6$_B$), 4.26 (1H, a-q, *J* ≈ 4.5, H-5$_A$), 4.35 (1H, ddd, *J* 9.1, 4.5, 1.8, H-5$_B$), 4.52–4.58 (4H, m, H-2$_A$, -2$_B$, -4$_A$, -4$_B$), 4.88 (1H, dd, *J* 6.1, 2.3, H-3$_A$ or -3$_B$), 4.93 (1H, dd, *J* 6.3, 2.9, H-3$_B$ or H-3$_A$), 5.11 [1H, sept, *J* 6.3, $CH(CH_3)_2$], 7.42 (1H, dd, *J* 7.2, 4.5, NH); δ_C ($CDCl_3$; 126 MHz) 21.6, 21.7 [2 × q, $CH(CH_3)_2$], 23.5, 23.6, 23.9, 23.9, 24.9, 24.9, 34.7, 34.7, 36.6, 37.0 (10 × t, CH_2, cyclohexylidene), 40.3 (t, CH_2NH), 52.4 (t, CH_2N_3), 69.5 [d, $OCH(CH_3)_2$], 81.1, 82.3, 83.3, 83.9, 84.0, 84.0, 84.5, 84.7 (8 × d, C-2$_A$, -2$_B$, -3$_A$, -3$_B$, -4$_A$, -4$_B$, -5$_A$, -5$_B$), 114.5 (s, O–C–O), 115.0 (s, O–C–O), 169.8 (s, C=O), 171.1 (s, C=O); *m/z* (APCI+) 565 (M + H$^+$, 40%).

Continued elution of the flash column (ethyl acetate–hexane 3 : 1) gave the lactam **22** (0.011 g, 14%).

Deprotected dimer, isopropyl 2,5-anhydro-6-(2,5-anhydro-6-azido-6-deoxy-D-allonamido)-6-deoxy-D-allonate 7. The cyclohexylidene-protected dimer **4** (0.030 g, 5.3 × 10^{-5} mol) was dissolved in a mixture of $CHCl_3$–TFA (1 : 1, 2 mL) to which water (2 drops) and propan-2-ol (2 drops) were also added. After stirring of the mixture for 30 min, TLC analysis (11% MeOH in $CHCl_3$) showed complete consumption of starting material (R_f 0.8) and two product spots (R_f 0.3 and 0.1). Concentration of the reaction mixture *in vacuo* (with toluene co-evaporation) and mass spectral analysis indicated the products to be the monodeprotected species with some of the fully deprotected azido isopropyl ester **7**. The crude product mixture was subjected to the same reaction conditions for 5 h. This procedure was continued until mass spectral analysis indicated complete conversion to the fully deprotected product **7**. Concentration *in vacuo* (with toluene co-evaporation) yielded a residue which was purified by flash chromatography (10% MeOH in $CHCl_3$) to give the deprotected dimer **7** (0.017 g, 81%), $[\alpha]_D^{24}$ +28.4 (*c* 0.29 in MeOH) [HRMS *m/z* (CI+) Found: 405.1612 (M + H$^+$). $C_{15}H_{25}N_4O_9$ requires *m/z*, 405.1622]; ν_{max} (KBr disc) 3500–3200 (NH, OH), 2106 (N_3), 1724 (C=O, ester), 1674, 1652 (C=O, amide I), 1534 (C=O, amide II) cm^{-1}; δ_H (CD_3OD; 500 MHz) 1.30 (3H, d, *J* 6.3, $CHCH_3$), 1.31 (3H, d, *J* 6.3, $CHCH_3$), 3.51 (1H, dd, *J* 14.0, 6.0, H-6$_B$), 3.59 (1H, dd, *J* 14.0, 4.1, H′-6$_B$), 3.68 (1H, dd, *J* 13.2, 3.7, H-6$_A$), 3.71 (1H, dd, *J* 13.2, 4.8, H′-6$_A$), 3.89 (1H, dd, *J* 7.0, 5.0, H-4$_A$ or 4$_B$), 3.90 (1H, dd, *J* 7.5, 5.0, H-4$_B$ or -4$_A$), 4.01 (2H, m, H-5$_A$, -5$_B$), 4.16 (1H, dd, *J* 5.0, 2.8, H-3$_A$ or -3$_B$), 4.17 (1H, dd, *J* 5.2, 2.9, H-3$_B$ or -3$_A$), 4.29 (1H, d, *J* 2.8, H-2$_A$), 4.33 (1H, d, *J* 2.8, H-2$_B$), 5.08 [1H, sept, *J* 6.3, $CH(CH_3)_2$]; δ_C (CD_3OD; 125.8 MHz) 21.9, 22.0 [2 × q, $CH(CH_3)_2$], 41.8 (t, C-6$_B$), 53.1 (t, C-6$_A$), 70.5 [d, $OCH(CH_3)_2$], 73.0, 73.6 (2 × d, 2 × C-4), 75.8, 76.1 (2 × d, 2 × C-3), 82.5, 82.5 (2 × d, 2 × C-5), 84.0 (d, C-2$_B$), 85.5 (d, C-2$_A$), 172.8 (s, O–C=O), 173.1 (s, NH–C=O); *m/z* (APCI+) 405 (M + H$^+$, 100%), 363 (M + H$^+$ − Pr^i, 10).

The protected tetramer, isopropyl 2,5-anhydro-6-[2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido]-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate 5. Aq. sodium hydroxide (1 M; 0.13 mL, 0.13 mmol) was added to a stirred solution of the protected dimer **4** (0.065 g, 0.12 mmol) in 1,4-dioxane (0.6 mL)–water (0.1 mL). TLC (ethyl acetate–hexane 1 : 1) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.0). The solvent was removed *in vacuo* (co-evaporation with toluene), the residue was dissolved in 1,4-dioxane (0.5 mL)–water (1 mL), and the solution was stirred with Amberlite IR-120 (H^+) resin for 15 min. The resin was removed by filtration and the filtrate was concentrated to give crude dimer acid **31**.

A solution of dimer **4** (0.065 g, 0.12 mmol) in propan-2-ol (0.3 mL) was stirred with palladium black (6 mg, 10%-wt) under a hydrogen atmosphere. After 4 h, TLC (ethyl acetate–hexane 1 : 1) indicated conversion of the starting material (R_f 0.5) to the amine **32** as the major product (R_f 0.0). The reaction mixture was filtered through Celite (eluted with Pr^iOH) and concentrated to give crude dimer amine **32**.

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.055 g, 0.18 mmol) was added to a stirred solution of the crude dimer acid **31** (0.12 mmol), 1-hydroxybenzotriazole (0.024 g, 0.18 mmol) and diisopropylethylamine (31 μL, 0.023 g, 0.18 mmol) in dichloromethane (0.6 mL) at 0 °C. The mixture was stirred for 30 min under a nitrogen atmosphere, and then a solution of the crude dimer amine **32** (0.12 mmol) in DCM (0.8 mL) was added. The reaction mixture was allowed to warm to room temperature overnight. TLC (ethyl acetate–hexane 1 : 1) indicated the formation of a major product (R_f 0.2). The reaction mixture was diluted with DCM (40 mL) and washed with 0.5 M HCl (1 × 20 mL). The aqueous layer was further extracted with DCM (2 × 20 mL). The combined DCM phases were washed with pH 7 buffer, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (ethyl acetate–hexane 1 : 1) to yield the tetramer **5** (0.081 g, 65%), $[\alpha]_D^{25}$ +43.2 (*c* 1.59 in $CHCl_3$); ν_{max} (thin film) 3307 (NH), 2105 (N_3), 1740 (C=O, ester), 1667 (C=O, amide I), 1539 (C=O, amide II) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.28 [6H, a-d, *J* 6.2, $CH(CH_3)_2$], 1.30–1.80 (40H, m, cyclohexylidene 20 × CH_2), 3.33 (1H, m, H′-6_B), 3.35 (1H, m, H′-6_D), 3.42 (1H, dd, *J* 13.3, 6.2, H′-6_A), 3.48 (1H, dd, *J* 13.7, 6.6, H-6_D), 3.54 (2H, m, H_2-6_C), 3.64 (1H, dd, *J* 13.2, 3.6, H-6_A), 3.74 (1H, ddd, *J* 14.0, 9.6, 8.7, H-6_B), 4.11 (1H, a-dt, *J* 9.6, 3.6, H-5_B), 4.19 (1H, a-dt, *J* 8.2, 4.2, H-5_C), 4.28 (1H, a-dt, *J*, 6.3, 4.1, H-5_A), 4.29 (1H, a-dt, *J* 6.9, 2.4, H-5_D), 4.40 (1H, dd, *J*, 5.7, 4.9, H-4_B), 4.48 (1H, dd, *J* 6.2, 4.2, H-4_C), 4.50 (1H, d, *J* 2.6, H-2), 4.51 (2H, 2 × d, $J \approx 2.2$, 2 × H-2), 4.53 (1H, d, *J* 2.0, H-2), 4.55 (1H, dd *J* 6.4, 3.7, H-4_A), 4.60 (1H, dd, *J* 6.2, 2.4, H-4_D), 4.84 (1H, dd, *J* 6.2, 2.6, H-3_D), 4.87 (1H, dd *J* 6.4, 2.7, H-3_C), 4.88 (1H, dd, *J* 5.7, 2.4, H-3_B), 4.93 (1H, dd, *J* 6.3, 2.8, H-3_A), 5.07 [1H, sept, $OCH(CH_3)_2$], 7.21 (1H, dd, *J* 8.1, 4.8, NH_B), 8.04 (1H, a-t, *J* 5.9, NH_D), 8.10 (1H, a-t, *J* 6.1, NH_C); δ_H (d_5-pyridine; 500 MHz)[32] 8.96 (1H, a-t, *J* 6.2, NH), 9.02 (1H, a-t, *J* 5.9, NH) and 9.24 (1H, a-t, *J* 6.1, NH); δ_C ($CDCl_3$; 100.6 MHz) 21.7, 21.7 [2 × q, $CH(CH_3)_2$], 23.5, 23.6, 23.9, 34.6, 34.7, 34.8, 36.7, 36.9, 37.2 (9 × t, cyclohexylidene, 20 × CH_2), 40.6, 41.7, 42.0 (3 × t, 3 × CH_2NH), 51.8 (t, CH_2N_3), 69.5 [d, $OCH(CH_3)_2$], 80.7, 81.1, 81.6, 82.6, 83.3, 83.5, 83.8, 83.8, 84.0, 84.1, 84.4, 84.5, 85.3, 85.8 (14 × d, 16 × CHO), 114.6, 114.7, 115.0, 115.1 (4 × s, 4 × O–C–O), 170.6, 170.7, 170.7, 171.3 (4 × s, 4 × C=O); (^{15}N) ($CDCl_3$; 50.7 MHz) 107.2 (NH_D), 108.0 (NH_B), 108.8 (NH_C); *m*/*z* (APCI+) 1043 ($M + H^+$), 1065 ($M + Na^+$); *m*/*z* (ES+) 1084.45 ($M + K^+$, 4%), 1083.47 ($M + K^+$, 15), 1082.45 ($M + K^+$, 31), 1081.50 ($M + K^+$, 52), 1068.47 ($M + Na^+$, 4), 1067.46 ($M + Na^+$, 20), 1066.50 ($M + Na^+$, 57), 1065.54 ($M + Na^+$, 100), 1063.03 ($[2M + H + K]^{2+}$, 12), 1045.49 ($M + H^+$, 8), 1044.55 ($M + H^+$, 28), 1043.57 ($M + H^+$, 49), (isotope distribution).

Table 1 δ_H-Values for tetramer **5** ($CDCl_3$) from 2D NMR experiments (COSY, TOCSY, HMQC, HMBC)

Ring	NH	H-2[a]	H-3	H-4	H-5	H-6/H′-6
A		[4.50,	4.93	4.55	4.28	3.42/3.64
B	7.21	4.51, 4.51, 4.53(B)]	4.88	4.40	4.11	3.33/3.74
C	8.10		4.87	4.48	4.19	3.54/3.54
D	8.04		4.84	4.60	4.29	3.35/3.48

[a] H-2 Assignments other than HB not confirmed to a particular ring system

Deprotected tetramer, isopropyl 2,5-anhydro-6-[2,5-anhydro-6-azido-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-6-deoxy-D-allonamido]-6-deoxy-D-allonate 8. Cyclohexylidene-protected tetramer **5** (0.015 g, 1.4×10^{-5} mol) was dissolved in a mixture of $CHCl_3$–TFA (1 : 1; 1 mL) to which water (1 drop) and propan-2-ol (1 drop) were also added. After stirring of the mixture for 3 h, concentration of the reaction *in vacuo* (with toluene co-evaporation) enable mass spectral analysis. A mixture of partly deprotected species was observed. The crude product mixture was subjected to the same reaction conditions repeatedly until mass spectral analysis indicated almost complete conversion to the fully deprotected product **8**. The final residue obtained was purified by flash chromatography (60% $CHCl_3$, 30% MeOH, 5% water, 3% AcOH) to give the deprotected tetramer **8** (0.010 g, 100%), $[\alpha]_D^{25}$ +47.1 (*c* 0.48 in MeOH); ν_{max} (thin film) 3500–3200 (NH, OH), 2101 (N_3), 1724 (C=O, ester), 1654 (C=O, amide I), 1546 (C=O, amide II) cm^{-1}; δ_H (CD_3OH; 500 MHz) 1.25 (3H, d, *J* 6.3, $CHCH_3$), 1.26 (3H, d, *J* 6.3, $CHCH_3$), 3.38 (1H, ddd, *J* 13.8, 4.8, 3.3, H′-6_B), 3.44 (1H, a-dt, *J* 13.8, 5.4, H′-6_D), 3.56 (2H, m, H_2-6_C), 3.59 (1H, m, H-6_D), 3.61 (1H, m, H′-6_A), 3.68 (1H, m, H-6_B), 3.70 (1H, m, H-6_A), 3.81 (1H, dd, *J* 7.1, 4.7, H-4_B), 3.86 (1H, dd, *J* 7.0, 5.0, H-4_C), 3.89 (1H, dd, *J* 7.7, 4.9, H-4_A), 3.91 (1H, dd, *J* 6.7, 5.0, H-4_D), 3.97 (1H, m, H-5_B), 3.99 (1H, m, H-5_C), 4.00 (1H, m, H-5_D), 4.02 (1H, m, H-5_A), 4.13 (1H, dd, *J* 5.0, 3.3, H-3_D), 4.19 (1H, m, H-3_C), 4.20 (1H, m, H-3_A), 4.21 (1H, m, H-3_B), 4.24 (1H, d, *J* 2.7, H-2_B), 4.25 (1H, d, *J* 2.9, H-2_C), 4.27 (1H, d, *J* 3.3, H-2_D), 4.29 (1H, d, *J* 2.7, H-2_A), 5.03 [1H, sept, *J* 6.3, $OCH(CH_3)_2$], 8.07 (1H, dd, *J* 7.8, 4.9, NH_B), 8.36 (1H, a-t, *J* 5.9, NH_D), 8.53 (1H, a-t, *J* 6.2, NH_C); δ_H (d_5-pyridine; 500 MHz)[32] 8.68 (1H, dd, *J* 8.0, 4.6, NH), 9.06 (1H, a-t, *J* 5.9, NH), 9.26 (1H, a-t, *J* 6.2, NH); δ_H (10% D_2O–H_2O; 500 MHz)[32] 8.18 (br s, NH), 8.25 (br s, NH), 8.40 (br t, *J* 5.5, NH); δ_C (CD_3OD; 125.8 MHz) 20.7, 20.7 [2 × q, $CH(CH_3)_2$], 40.9 (t, C-6_D), 41.5 (t, C-6_C), 41.8 (t, C-6_B), 52.0 (t, C-6_A), 68.9 [$OCH(CH_3)_2$], 71.3 (d, C-4_A), 72.8 (d, C-4_D), 73.0 (d, C-4_B), 73.0† (d, C-4_C), 74.6 (d, C-3_D), 74.9† (d, C-3_A), 74.9† (d, C-3_B), 74.9†(d, C-3_C), 81.2† (d, C-5_A), 81.2†; (d, C-5_C), 81.2† (d, C-5_D), 81.7 (d, C-5_B), 82.6 (d, C-2_D), 83.9† (d, C-2_B), 83.9† (d, C-2_C), 84.2 (d, C-2_A), 171.2 (s, C-1_D), 172.1 (s, C-1_C), 172.7† (s, C-1_B), 172.7† (s, C-1_A); *m*/*z* (ES+) 761.48 ($M + K^+$, 7%), 747.44 ($M + Na^+$, 9), 746.44 ($M + Na^+$, 30) 745.49 ($M + Na^+$, 100), 742.48 ($[2M + H + K]^{2+}$, 4) 723.40 ($M + H^+$, 7) (isotope distribution).

The octamer, isopropyl 2,5-anhydro-6-[2,5-anhydro-6-azido-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-

† Values obtained from broad/overlapping HSQC/HMBC crosspeaks.

Table 2 δ_H-Values for tetramer **8** (CD_3OH) from 2D NMR experiments (DQFCOSY, TOCSY, HSQC, HMBC)

Ring	NH	H-2[a]	H-3	H-4	H-5	H-6/H′-6
A		4.29	4.20	3.89	4.02	3.61/3.70
B	8.07	4.24	4.21	3.81	3.97	3.38/3.68
C	8.53	4.25	4.19	3.86	3.99	3.56/3.56
D	8.36	4.27	4.13	3.91	4.00	3.44/3.59

[a] Assigned *via* TOCSY crosspeaks from H-2 to H-4.

D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido-(*N*→6)-2,5-anhydro-3,4-*O*-cyclohexylidene-6-deoxy-D-allonamido]-3,4-*O*-cyclohexylidene-6-deoxy-D-allonate 6. Aq. sodium hydroxide (1 M; 36 μL, 3.6×10^{-5} mol) was added to a stirred solution of tetramer **5** (0.034 g, 3.3×10^{-5} mol) in 1,4-dioxane (0.3 mL)–water (0.1 mL). After 1 h, TLC (ethyl acetate–hexane 1:1) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.0). The solvent was removed *in vacuo* (co-evaporated with toluene), the residue was dissolved in 1,4-dioxane (0.5 mL)–water (0.5 mL), and the solution was stirred with Amberlite IR-120 (H^+) resin for 10 min. The resin was removed by filtration and the filtrate was concentrated to give crude tetramer acid **33** (0.033 g, 100%).

A solution of tetramer **5** (0.038 g, 3.6×10^{-5} mol) in propan-2-ol (0.2 mL) was stirred with palladium black (4 mg, 10%-wt) under a hydrogen atmosphere. After 4 h, TLC (ethyl acetate–hexane 1:1) indicated a mixture of starting material (R_f 0.2) and product (R_f 0.0). Additional palladium black (6 mg) was added at this time and again after 6 h. The reaction mixture was then stirred overnight, when TLC analysis showed an absence of starting material. The reaction mixture was filtered through Celite and the product was eluted with propan-2-ol. Concentration *in vacuo* gave crude tetramer amine **34** (0.032 g, 86%).

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (9.5 mg, 4.9×10^{-5} mol) was added to a stirred solution of the crude tetramer acid **33** (3.3×10^{-5} mol), 1-hydroxybenzotriazole (6.6 mg, 4.9×10^{-5} mol) and diisopropylethylamine (8.5 μL, 6.3 mg, 4.9×10^{-5} mol) in dichloromethane (0.2 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C under a nitrogen atmosphere, and then a solution of the crude tetramer amine **34** (3.6×10^{-5} mol) in dichloromethane (0.2 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. TLC (ethyl acetate–hexane 3:2) indicated the formation of a major product (R_f 0.2). The reaction mixture was diluted with dichloromethane (50 mL) and washed with 0.5 M HCl (1 × 20 mL). The aqueous layer was further extracted with dichloromethane (3 × 15 mL). The combined dichloromethane phases were washed with pH 7 buffer, dried over $MgSO_4$, and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (ethyl acetate–hexane 3:2) to yield the octamer **6** (0.034 g, 52%), $[\alpha]_D^{24}$ +65.9 (*c* 0.79 in $CHCl_3$); ν_{max} (thin film) 3307 (NH), 2105 (N_3), 1737 (C=O, ester), 1662 (C=O, amide I), 1539 (C=O, amide II) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 1.27 (3H, d, *J* 6.3, CHCH_3), 1.28 (3H, d, *J* 6.3, CHCH_3), 1.30–1.78 (80H, m, 40 × CH_2), 3.24–3.29 (1H, m, H-6_B), 3.37–3.57 (13H, m, 13 × H-6), 3.67 (1H, dd, *J* 13.3, 3.4, H′-6_A), 3.71–3.78 (1H, m, H′-6_B), 4.09–4.22 (6H, m, 6 × H-5), 4.25–4.32 (2H, m, H-5_A, -5_H), 4.36–4.43 (5H, m, 5 × H-4), 4.45–4.49 (3H, m, 1 × H-4, 2 × H-2), 4.50–4.53 (5H, m, 5 × H-2), 4.56 (1H, br s, H-2_B), 4.57 (1H, dd, *J* 6.4, 3.6, H-4_A), 4.65 (1H, dd, *J* 6.3, 2.6, H-4_H), 4.84 (1H, dd, *J* 6.3, 2.8, H-3_H), 4.88–4.96 (8H, m, 8 × H-3), 5.06 [1H, sept, *J* 6.3, C*H*(CH_3)$_2$], 7.12 (1H, dd, *J* 8.8, 4.6, NH_B), 8.26 (1H, a-t, *J* 6.0, NH_H), 8.52 (1H, a-t, *J* 6.4, NH), 8.56 (1H, a-t, *J* 6.2, NH), 8.64 (1H, a-t, *J* 6.4, NH), 8.72 (1H, a-t, *J* 6.4, NH), 8.80 (1H, a-t, *J* 6.4, NH); δ_C ($CDCl_3$; 100.6 MHz)[33] 21.9, 21.9 [2 × q, CH(*C*H_3)$_2$], 23.8, 24.2, 25.2, 29.9, 35.1, 37.5 (6 × t, cyclohexylidene, 40 × CH_2), 40.7, 42.3, 42.7 (3 × t, 7 × CH_2NH), 52.2 (t, CH_2N_3), 69.5 [d, O*C*H(CH_3)$_2$], 81.0 (C-4_A), 81.2, 81.6, 81.8 (C-4), 83.0 (C-4_H), 83.8 (C-3_H), 83.5, 84.2, 84.3, 84.6 (C-3), 84.3 (C-2_B), 84.5, 84.7 (C-2), 84.2 (C-5_A), 84.6 (C-5_H), 86.3, 86.9 (C-5), 87.0 (C-5_B); (^{15}N) ($CDCl_3$; 50.7 MHz) 107.4 (NH_H), 108.8 (NH_B), 110.1 (NH), 111.9 (NH), 112.0 (NH), 112.0 (NH), 112.5 (NH); *m/z* (ES+) 1021.85 ([M + H + K]$^{2+}$, 6%), 1021.35 ([M + H + K]$^{2+}$, 15), 1020.84 ([M + H + K]$^{2+}$, 31), 1020.36 ([M + H + K]$^{2+}$, 76), 1019.82 ([M + H + K]$^{2+}$, 100), 1019.34 ([M + H + K]$^{2+}$, 87), 781.69 ([M + H + K]$^{2+}$-dimer, 5), 781.24 ([M + H + K]$^{2+}$-dimer, 13), 780.73 ([M + H + K]$^{2+}$-dimer, 24), 780.24 ([M + H + K]$^{2+}$-dimer, 31), 693.62 ([M + H + K2]$^{3+}$, 11), 692.95 ([M + H + K2]$^{3+}$, 32), 692.74 ([M + H + K2]$^{3+}$, 27) (isotope distribution); *m/z* (ES+, 10 mM NH_4OAc) 1002.96 ([M + 2H]$^{2+}$, 5%), 1002.43 ([M + 2H]$^{2+}$, 12), 1001.96 ([M + 2H]$^{2+}$, 32), 1001.43 ([M + 2H]$^{2+}$, 66), 1000.96 ([M + 2H]$^{2+}$, 100), 1000.44 ([M + 2H]$^{2+}$, 81), (isotope distribution).

Table 3 δ_H-Values for octamer **6** ($CDCl_3$) from 2D NMR experiments (COSY, TOCSY, HMQC, HMBC)

Ring	NH	H-2	H-3	H-4	H-5	H-6/H′-6
A		4.49	4.93	4.57	4.30	3.40/3.67
B	7.12	4.56	4.95	4.39	4.12	3.27/3.76
C[a]	8.80		4.95	4.41	4.19	3.42/3.56
D[a]	8.72	(4.50,	4.91	4.43	4.18	3.48/3.53
E[a]	8.64	4.51, 4.52,	4.97	4.42	4.18	3.49/3.49
F[a]	8.56	4.52,	4.90	4.47	4.16	3.47/3.56
G[a]	8.52	4.53)[b]	4.94	4.42	4.21	3.52/3.56
H	8.26	4.48	4.84	4.65	4.28	3.42/3.42

[a] Rings C, D, E, F and G are randomly assigned and therefore interchangeable. However, the connectivities within the ring systems were established by a TOCSY NMR experiment. [b] H-2 connectivities to the remainder of the ring system were not determined for rings C, D, E, F or G due to signal overlap.

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