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Towards hydroxylated nylon 6: oligomers from a protected 6-amino-6-deoxy-D-allonate

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Abstract—The first synthesis of linear oligomers (a dimer, tetramer, hexamer and octamer) of fully hydroxylated analogues of nylon 6 by iterative formation of peptide bonds from a protected 6-amino-6-deoxy-D-allonate monomer is reported.

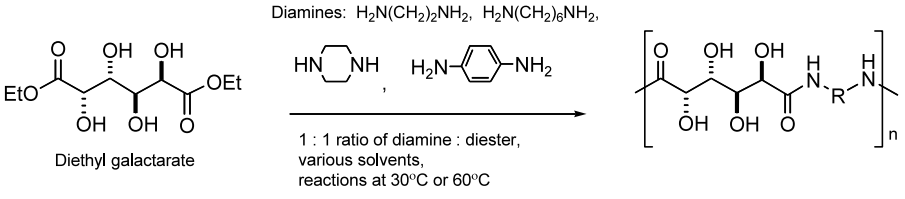
1. Introduction

Although in the past the majority of commercially available synthetic biodegradable polymers have been limited to polyesters, several different types of biodegradable polymers are currently being evaluated for a wide range of practical uses.[1] Biodegradability is sought after in many applications, above all in the preparation of environmentally friendly polymers[2] and biomedical materials for temporary surgical use and in drug delivery.[3] For example, polyhydroxyalkanonate derivatives have been developed as biodegradable suture strings[4] and as polymeric scaffolds for the controlled release of drugs such as dexamethasone.[5]

Polyhydroxylated nylon 6,6[6] and related compounds constitute a class of biodegradable polymers which has attracted considerable attention with respect to their synthesis and structure. Such materials, formed by condensation of diamines and aldaric acid derivatives, have been extensively studied[7,8] and are exemplified by the reactions of diethyl galactarate with a range of diamines.[9,10]

Even though synthetic[11–14] and structural[15,16] studies on such [6,6] nylon analogues are extensive, there are essentially no reports of the coupling of sugar 1,6-diacids with sugar 1,6-diamines. Recent studies also include the synthesis of stereoregular polymers derived from glucaric acid and a series of alkylene diamines,[17] polyurethanes from L-gulonic acid-derived diols and diisocyanates,[18] and investigation of the properties of polymers formed from 1,6-diamino alditols with alkyl dioic acids.[19] Similar condensations of diamines with other hydroxyacids have been reported.[20] A synthesis of a monomer for the formation of polymers derived from a sugar β-amino acid has been reported[21] but there have been no subsequent reports of either oligomers or polymers of such compounds.

In contrast to the extensive literature on polyhydroxylated nylon 6,6, there have been no reports of the synthesis of oligomeric or polymeric sugar analogues of polyhydroxylated nylon 6. Recently a synthesis of 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid as a precursor of a stereoregular polyamide has been reported but no oligomers or polymers were described.[22] Undoubtedly one reason for this is that access to polyhydroxylated 6-aminohexanoic acid monomers usually requires longer synthetic sequences. Additionally, such monomers are prone to the formation of lactams;[23] whereas polymerisation of capro-



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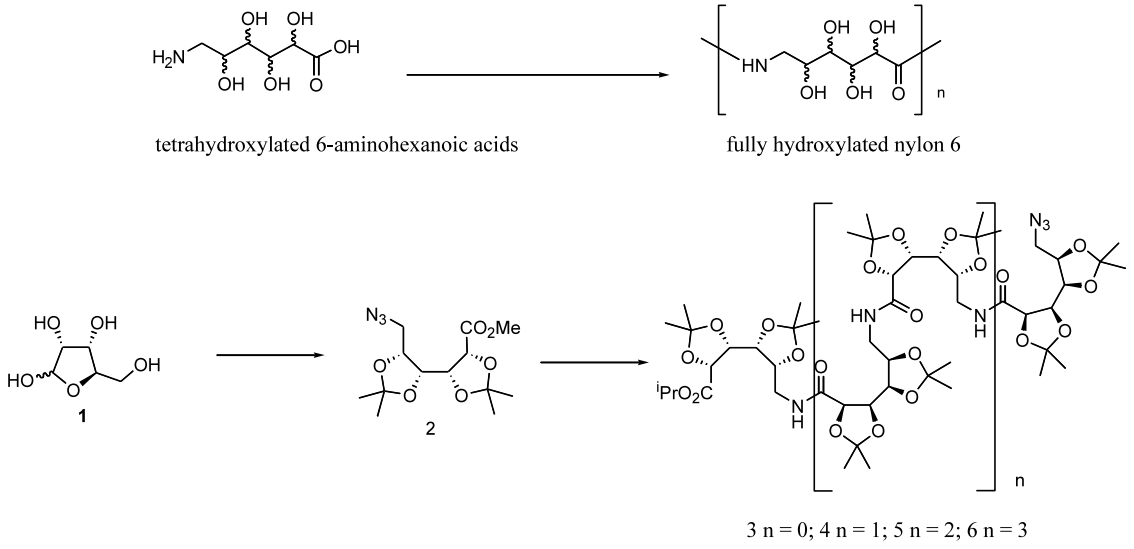
lactam is the standard method for the synthesis of nylon 6, tetrahydroxylated lactams undergo other reactions such as dehydration before polymerisation takes place. The complex mixtures which result preclude convincing characterisation of the novel polymers which are probably formed.

The potential of sugar amino acids[24] (SAA) as monomers[25] for new biomaterials[26] has been recognized.[27] Conformationally locked[28,29] ring-templated SAA have provided a rich mine of building blocks for the production of foldamers,[30] short oligomers with a predisposition towards the generation of secondary structures.[31] 6-Amino-6-deoxyaldonic acids constitute a class of SAA which should provide monomers for hydroxylated nylon 6.

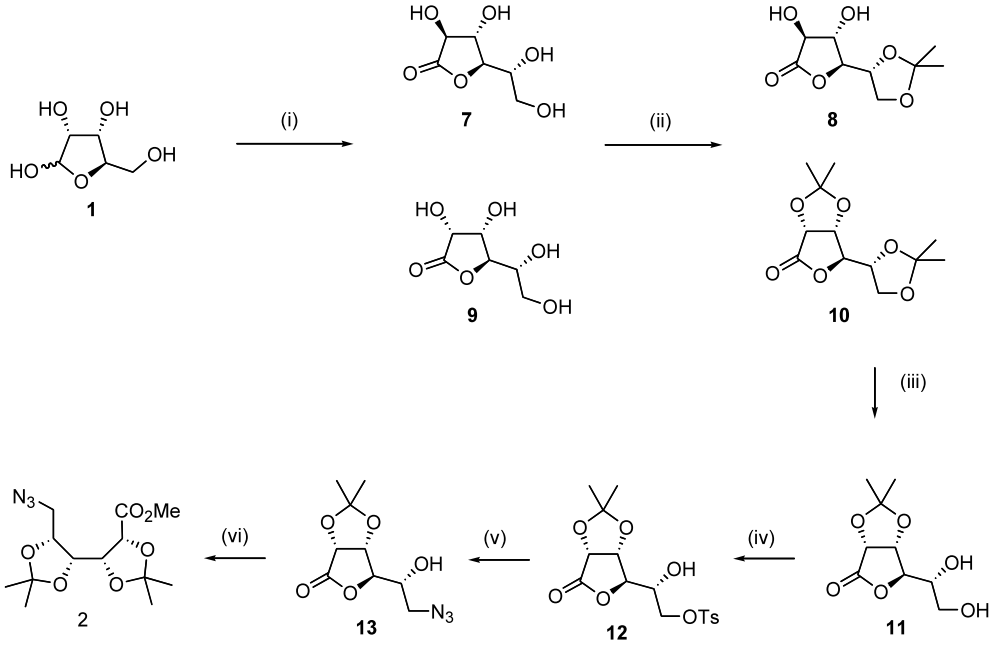
This paper reports the synthesis of homogeneous well-defined oligomers of hydroxylated nylon 6 (Scheme 1) from D-ribose **1** via the key azido-ester intermediate **2**; the dimer **3**, tetramer **4**, hexamer **5** and octamer **6** are the first reported examples of oligomers of tetrahydroxylated 6-aminohexanoic acids as polyhydroxylated nylon 6 analogues.

2. Synthesis of the monomeric scaffold 2

Access to the building block **2** requires the synthesis of the thermodynamic monoacetonide of allono-lactone **11** for the introduction of an azide functionality at C-6 (Scheme 2).



Scheme 1.



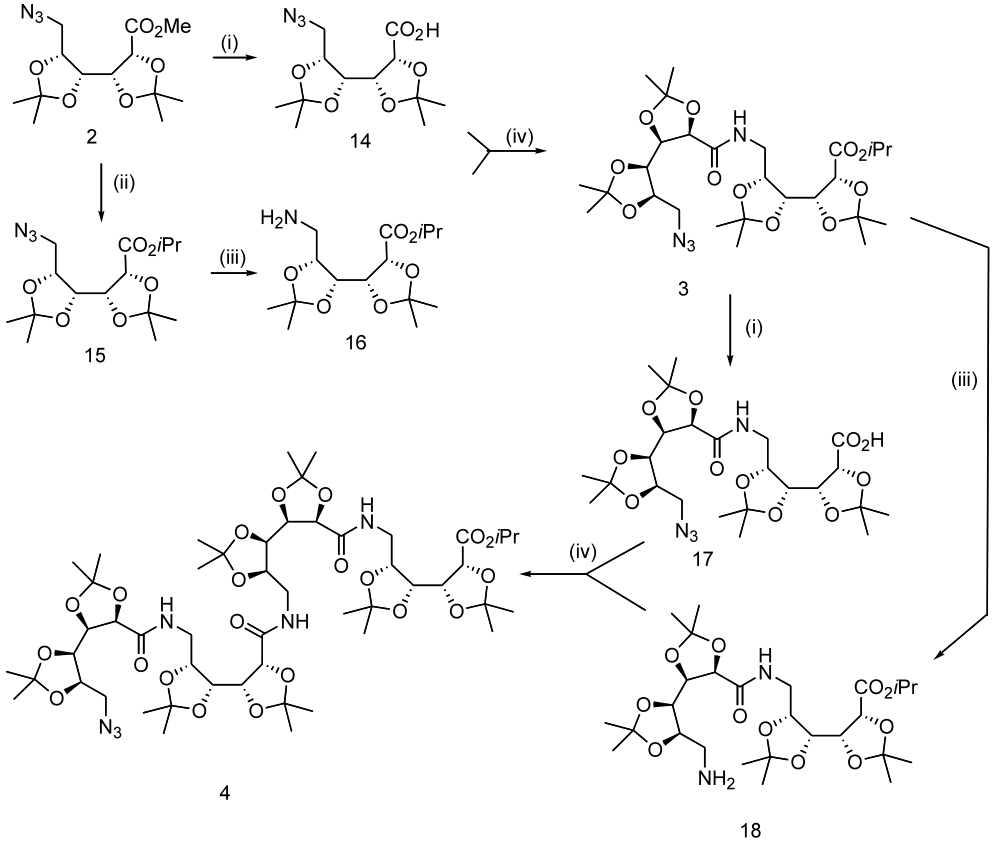
Scheme 2. *Reagents and conditions*: (i) NaCN, H_2O, 0°C, 24 h, then 80°C, 8 h; (ii) Me_2CO, conc. H_2SO_4; (iii) 80% $AcOH/H_2O$, 45°C; (iv) TsCl, pyridine, 3 Å sieves, rt; (v) NaN_3, DMF, 65°C; (vi) $Me_2C(OMe)_2$, CSA, Me_2CO, 50°C.

The Kiliani ascension of D-ribose **1** was effected using a minor modification of a literature procedure.[32] Treatment of an aqueous solution of ribose with sodium cyanide initially at 0°C and subsequently at 80°C afforded, after lactonisation, a crude mixture of D-allono- **9** and D-altrono- **7** lactone. This mixture, without any purification, was treated with acetone in the presence of concentrated sulfuric acid to give an easily separable mixture of the diacetonide of D-allono-1,4-lactone **10** in 30% overall yield together with the more polar monoacetonide 5,6-*O*-isopropylidene-D-altrono-1,4-lactone **8**. Treatment of the *allo* diacetonide **10** with aqueous acetic acid resulted in selective hydrolysis of the 5,6 acetonide to afford the thermodynamic monoacetonide **11** in 52% with recovery of 35% of starting material; this is a relatively unselective hydrolysis of the terminal acetonide and the best overall yields were obtained by stopping the reaction before all the starting material had been consumed. Esterification of the monoacetonide **11** with toluenesulfonyl chloride in pyridine gave selective formation of the primary tosylate **12** in 73% yield. Subsequent reaction of the tosylate **12** with sodium azide in DMF afforded the azidolactone **13** in 81% yield. Finally, treatment of **13** with dimethoxypropane in acetone in the presence of camphor sulfonic acid (CSA) caused concomitant lactone opening and acetonide protection of the resulting 4,5-diol to produce the open chain ester **2** in 63% yield; the conditions for this conversion are similar to those used for the formation of an open chain derivative from galactonolactone.[33] The overall yield of the key intermediate methyl ester **2** from the diacetonide **10** was 20%; **2** is readily available on a gram scale.

3. Oligomers-dimer 3, tetramer 4, hexamer 5 and octamer 6 of aminoallonate 2

The azidoester **2** is the key building block for the controlled formation of oligomeric hydroxylated [6] nylons and requires reduction of the azide function to give the amino component and hydrolysis of the ester to give the carboxylic acid component. However, hydrogenation of **2** produced the corresponding amine which spontaneously closed to the corresponding lactam. Consequently, this was not a convenient procedure for the synthesis of well-defined oligomers.

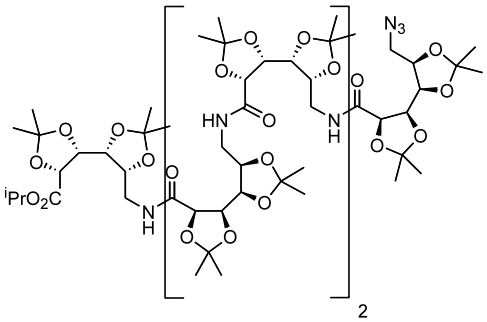
Thus it was necessary first to exchange the methyl ester for the more hindered isopropyl ester; reaction of **2** with isopropanol in the presence of potassium carbonate for 15 h under reflux induced transesterification to afford the isopropyl ester **15** in 56% yield (Scheme 3). The methyl ester **2** was hydrolysed by sodium hydroxide in aqueous dioxane to give, after stirring with acid ion exchange resin, the carboxylic acid **14**. Hydrogenation of the azido-isopropyl ester **15** in the presence of palladium black gave the corresponding amine **16**. The



Scheme 3. *Reagents and conditions*: (i) NaOH (aq.), dioxane, then Amberlite IR-120 H^+; (ii) *iso*-PrOH, K_2CO_3, 90°C; (iii) H_2, Pd black, EtOAc; (iv) 1.5 equiv. EDCI, 1.5 equiv. HOBt, 1.5 equiv. DIPEA, CH_2Cl_2.

crude acid and amine were then coupled by standard reagents for the formation of peptide links. Activation of the carboxylic acid **14** by 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), followed by reaction with hydroxybenzotriazole (HOBt) in the presence of diisopropylethylamine (DIPEA), produced an activated ester; further reaction with the crude amine **16** formed the dimer **3** in an overall yield of 58%.

An iterative procedure allowed the formation of the tetramer **4**. Thus hydrolysis of the dimer **3** gave the crude acid **17** which was coupled with the crude amine **18** to give the tetramer **4** in an isolated yield of 53%.



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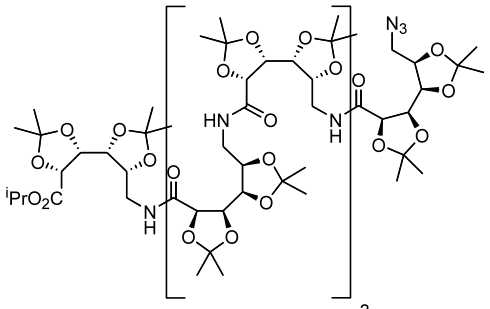

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Further iteration by coupling the acid **17** derived from the dimer with the amine obtained from reduction of the tetramer **4** gave the hexamer **5** in 45% yield. The octamer **6** was obtained in 41% yield by coupling the dimer acid **17** with the amine formed by reduction of the hexamer.

Little epimerisation appeared to take place during activation and coupling; in some cases, small amounts of possible epimeric products were obtained. However, the majority of product in all the oligomer preparations was homogeneous material as shown by ^{13}C and ^{1}H NMR data reported in Section 5.

4. Structural studies and summary

This paper describes the first synthesis of polyhydroxylated nylon 6 oligomers derived from a protected 6-amino-6-deoxy-D-allonic acid monomer. Structural studies by NMR and by CD experiments on the oligomers prepared in this paper provided no evidence for the formation of secondary structures. Analogous structures will be reported in a following paper[34] which describes the formation of linear oligomers from a 6-amino-6-deoxy-D-galactonic acid monomer, together with the formation of a cyclic tetramer.

5. Experimental

Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride and stored over dried 3 Å molecular sieves; hexane refers to 60–80°C petroleum ether; water was distilled. *N*,*N*-Dimethylformamide was purchased dry from the Aldrich Chemical Company in Sure/Seal™ bottles. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Reactions performed under an atmosphere of nitrogen or 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 were used as supplied, without prior purification. Thin-layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Products were visualised using a spray of 0.2% w/v cerium(IV) sulphate and 5% ammonium molybdate in 2 M sulphuric acid or 0.5% ninhydrin in methanol (particularly for amines). Flash column chromatography was performed on Sorbsil C60 40/60 silica, acidic ion-exchange chromatography was performed on Amberlite® IR-120 (H^+) and basic ion exchange chromatography was performed on Dowex® 1X8-400 (basic form). CMAW refers to the eluent system—chloroform:methanol:acetic acid:water (60:30:3:5). Melting points were recorded on a Köfler hot block and are corrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 500 or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) or where stated on a Bruker AC 200 (^{1}H: 200 MHz and ^{13}C: 50.3 MHz) or Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) spectrometer in deuterated solvent. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference and ^{13}C NMR spectra in D_2O were referenced to 1,4-dioxane (δ_C 67.4). ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform, or Perkin–Elmer Paragon 1000 spectrophotometer using thin films on NaCl plates (thin film). Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded on VG MassLab 20-250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers and high-resolution mass spectra (HRMS m/z) on a Micromass Autospec 500 OAT spectrometer. Techniques used were electrospray (ES), matrix-assisted laser desorption ionisation (MALDI), chemical ionisation (CI, NH_3), or atmospheric pressure

chemical ionisation (APCI) using partial purification by HPLC with 40:40:20 methanol:acetonitrile:water as eluent, as stated. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml.

5.1. 2,3:5,6-Di-*O*-isopropylidene-D-allono-1,4-lactone 10 and 5,6-*O*-isopropylidene-D-altrono-1,4-lactone 8

A solution of sodium cyanide (36 g, 0.73 mol) in water (300 ml) was added to a stirred solution of aqueous D-ribose **1** (79 g, 0.53 mol) at 0°C. The reaction mixture was stirred for 20 h then heated at 80°C for 2 days. After cooling, the mixture was passed down a column of Amberlite IR-120 (H^+) (approx. 1 kg), and eluted with water (approx. 3 l). The eluent was concentrated in vacuo affording D-allono-1,4-lactone **9** and D-altrono-1,4-lactone **7** as a dark brown viscous oil (94 g crude), used without further purification. Concentrated sulfuric acid (1.5 ml) was added dropwise to a stirred suspension of D-allono-1,4-lactone **10** and D-altrono-1,4-lactone **8** (12.0 g, crude) in acetone (400 ml) at room temperature. After 2 days, TLC (ethyl acetate) indicated conversion of the starting material (R_f 0.0) to a major product (R_f 0.6) and a minor product (R_f 0.9). The reaction mixture was neutralised with sodium carbonate (15 g, excess), filtered through Celite and purified by flash chromatography (ethyl acetate:hexane, 2:3) to yield 2,3:5,6-di-*O*-isopropylidene-D-allono-1,4-lactone **10** (5.26 g, 30.2%) as a white crystalline solid, mp 68–70°C (ethanol); $[\alpha]_D^{25} = -68.2$ (*c* 1.00 in $CHCl_3$) (lit.[35] mp 71–73°C, $[\alpha]_D^{23} = -67$); δ_H (500 MHz, $CDCl_3$): 1.32, 1.39, 1.45, 1.47 (4×3H, 4×s, 2×$C(CH_3)_2$), 3.89 (1H, dd, $J_{6,6'}$ 9.1 Hz, $J_{6,5}$ 5.1 Hz, H-6), 4.17 (1H, dd, $J_{6',5}$ 7.5 Hz, H-6′), 4.31 (1H, ddd, $J_{4,5}$ 3.9 Hz, H-5), 4.48 (1H, d, H-4), 4.72 (1H, d, $J_{3,2}$ 5.7 Hz, H-3), 4.76 (1H, d, H-2).

Continued elution gave a mixture of products containing 5,6-*O*-isopropylidene-D-altrono-1,4-lactone **8** and monoacetonides of D-allono-1,4-lactone.

5.2. 2,3-*O*-Isopropylidene-D-allono-1,4-lactone 11

The fully protected allono-lactone **10** (5.22 g, 20.2 mmol) was dissolved in aqueous acetic acid (125 ml, 80% v/v) and stirred under nitrogen at 45°C. After 3 h, TLC (ethyl acetate:hexane, 3:1) indicated partial conversion of the starting material (R_f 0.7) to a major (R_f 0.2) and a minor (R_f 0.0) product. The solvent was removed in vacuo (co-evaporation with toluene) and the residue purified by flash chromatography (ethyl acetate:hexane, 3:1) to yield 2,3-*O*-isopropylidene-D-allono-1,4-lactone **11** (2.31 g, 52.4%) as a white crystalline solid, mp 116–118°C; $[\alpha]_D^{25} = -72.7$ (*c* 1.1 in $(CH_3)_2CO$); ν_{max}(KBr): 3368 (b, OH), 1766 (C=O lactone) cm^{-1}; δ_H (400 MHz, $(CD_3)_2CO$): 1.36, 1.40 (2× 3H, 2×s, $C(CH_3)_2$), 3.70 (1H, dd, $J_{6,6'}$ 11.0 Hz, $J_{6,5}$ 6.3 Hz, H-6), 3.75 (1H, dd, $J_{6',5}$ 5.4 Hz, H-6′), 3.93 (1H, ddd, $J_{5,4}$ 2.6 Hz, H-5), 4.67 (1H, d, H-4), 4.76 (1H, d, $J_{3,2}$ 5.6 Hz, H-3), 4.98 (1H, d, H-2); *m*/*z* (APCI+): 219 (MH^+, 100%). A significant amount of recovered starting material (1.82 g, 34.9%) was recycled through this procedure.

5.3. 2,3-*O*-Isopropylidene-6-*O*-*p*-toluenesulfonyl-D-allono-1,4-lactone 12

The monoacetonide **11** (2.14 g, 9.84 mmol) was dissolved in dry pyridine (100 ml) and stirred under nitrogen at room temperature with molecular sieves (3 Å, 3.2 g) for 1 h. *p*-Toluenesulfonyl chloride (5.63 g, 29.5 mmol) was added and the mixture stirred for 5 h. TLC (ethyl acetate:hexane, 3:1) indicated conversion of the starting material (R_f 0.2) to a major product (R_f 0.8). The reaction mixture was filtered through Celite, eluting with dichloromethane, and the solvent removed in vacuo, co-evaporating with toluene. The residue was dissolved in ethyl acetate (300 ml) and washed with pH 7 buffer (40 ml). The organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (ethyl acetate:hexane, 1:2.5) to yield 2,3-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-D-allono-1,4-lactone **12** (2.68 g, 73%) as a yellow oil; $[\alpha]_D^{25} = -41.2$ (*c* 0.69 in $CHCl_3$); δ_H (400 MHz, $(CD_3)_2CO$): 1.35, 1.39 (2×3H, 2×s, $C(CH_3)_2$), 2.49 (3H, s, $ArCH_3$), 4.13 (1H, ddd, $J_{5,6}$ 6.3 Hz, $J_{5,6'}$ 4.6 Hz, $J_{5,4}$ 3.4 Hz, H-5), 4.22 (1H, m, H-6), 4.29 (1H, m, H-6′), 4.58 (1H, d, H-4), 4.77 (1H, d, $J_{3,2}$ 5.7 Hz, H-3), 4.92 (1H, d, H-2), 7.53 (2H, d, 2×ArH), 7.87 (2H, d, 2×ArH); *m*/*z* (APCI+): 373 (MH^+, 100%).

5.4. 6-Azido-6-deoxy-2,3-*O*-isopropylidene-D-allono-1,4-lactone 13

Sodium azide (702 mg, 10.8 mmol) was added to a stirred solution of the tosylate **12** (2.68 g, 7.2 mmol) in DMF (15 ml). The mixture was heated to 65°C and stirred under nitrogen for 3.5 h. TLC (ethyl acetate:hexane, 1:2) indicated conversion of the starting material (R_f 0.3) to a major product (R_f 0.7). The solvent was removed in vacuo (co-evaporation with toluene), the residue dissolved in ethyl acetate (150 ml) and washed with water (60 ml). The aqueous phase was washed with ethyl acetate (3×30 ml), the organic layers combined, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (ethyl acetate:hexane, 1:3) to yield 6-azido-6-deoxy-2,3-*O*-isopropylidene-D-allono-1,4-lactone **13** (1.42 g, 81.4%) as a white crystalline solid; mp 51°C; $[\alpha]_D^{25} = -68.8$ (*c* 0.95 in $CHCl_3$); ν_{max}(KBr): 2108 (N_3), 1784 (C=O) cm^{-1}; δ_H (400 MHz, $(CD_3)_2CO$): 1.39, 1.42 (2× 3H, 2×s, $C(CH_3)_2$), 3.60 (2H, m, H-6, H-6′), 4.09 (1H, m, H-5), 4.58 (1H, d, $J_{4,5}$ 3.5 Hz, H-4), 4.83, 5.03 (2×1H, 2×d, $J_{2,3}$ 5.7 Hz, H-2, H-3), 5.37 (1H, d, $J_{OH,5}$ 5.5 Hz, OH); *m*/*z* (APCI+): 216 ($M-N_2+H^+$, 100%).

5.5. Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonate 2

DL-Camphor sulfonic acid (380 mg, 1.64 mmol) was added to a stirred solution of the azide **13** (1.00 g, 4.12 mmol) in 2,2-dimethoxypropane (12 ml) and acetone (0.9 ml). The reaction mixture was stirred at 50°C for 15 h under an atmosphere of nitrogen. TLC (ethyl acetate:hexane 1:2) indicated partial conversion of the starting material (R_f 0.3) to a major product (R_f 0.7). Sodium hydrogencarbonate (1 g, excess) was added, the

reaction mixture stirred for 1 h and then filtered through Celite. The solvent was removed in vacuo and the residue purified by flash chromatography (ethyl acetate:hexane, 1:8) to yield methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonate **2** (815 mg, 63%) as a yellow oil; (HRMS: $M-N_2+H^+$: 288.144713. $C_{13}H_{22}NO_6$ requires: 288.144699); $[\alpha]_D^{25}=+31.9$ (*c* 0.95 in $CHCl_3$); ν_{max}(thin film): 2102 (N_3), 1755 (C=O, ester) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.29, 1.34, 1.45, 1.54 (12H, 4×s, 2×C(C$\underline{H}_3$)$_2$), 3.47 (2H, m, H-6, H-6′), 3.72 (3H, s, $CO_2C\underline{H}_3$), 4.13 (1H, dd, $J_{4,5}$ 6.0 Hz, $J_{4,3}$ 9.97 Hz, H-4), 4.30 (1H, m, H-5), 4.34 (1H, dd, $J_{3,2}$ 6.3 Hz, H-3), 4.71 (1H, d, H-2); δ_C (100.6 MHz, $CDCl_3$): 25.2, 25.5, 27.2, 27.7 (4×q, 2×C($\underline{C}H_3$)$_2$), 50.7 (t, C-6), 52.0 (q, $CO_2\underline{C}H_3$), 74.2, 74.9, 76.2, 76,7 (4×d, C-2, C-3, C-4, C-5), 109.7, 111.3 (2×s, 2×$\underline{C}$(CH$_3$)$_2$), 168.7 (s, C-1); *m*/*z* (APCI+ve): 288 ($M-N_2+H^+$, 100%).

5.6. Isopropyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonate 15

Potassium carbonate (217 mg, 1.57 mmol) was added to a stirred solution of the methyl ester **2** (413 mg, 1.31 mmol) in isopropyl alcohol (3 ml). The reaction was refluxed at 90°C under an atmosphere of nitrogen for 15 h. TLC (ethyl acetate:hexane 1:6) indicated partial conversion of the starting material (R_f 0.3) to a major product (R_f 0.5). The mixture was cooled, filtered through Celite and the solvent removed in vacuo. The residue was purified by flash chromatography (ethyl acetate:hexane, 1:10) to yield isopropyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonate **15** (252 mg, 56%) as a clear oil; (HRMS: $M-N_2+H^+$: 316.176013. $C_{15}H_{26}NO_6$ requires: 316.175997); $[\alpha]_D^{25}=+36.9$ (*c* 0.84 in $CHCl_3$); ν_{max}(thin film): 2103 (N_3), 1744 (C=O ester) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.28, 1.30 (2×3H, 2×d, $J_{vicinal}$ 1.9 Hz, OCH(C$\underline{H}_3$)$_2$), 1.37, 1.43, 1.45, 1.46 (4×3H, 4×s, 2×C(CH$_3$)$_2$), 3.58 (2H, m, H-6, H-6′), 4.06 (1H, dd, $J_{4,3}$ 9.6 Hz, $J_{4,5}$ 5.9 Hz, H-4), 4.35 (1H, dd, $J_{3,2}$ 5.3 Hz, H-3), 4.48 (1H, m, H-5), 4.44 (1H, d, H-2), 5.09 (1H, sep, *J* 6.3 Hz, OC$\underline{H}$(CH$_3$)$_2$); δ_C (100.6 MHz, $CDCl_3$): 21.6 (2×q, OCH($\underline{C}H_3$)$_2$), 25.4, 26.3, 27.5, 27.6 (4×q, 2×C($\underline{C}H_3$)$_2$), 50.3 (t, C-6), 69.3 (d, O$\underline{C}$H(CH$_3$)$_2$), 76.5, 77.2, 77.6, 78.7 (4×d, C-2, C-3, C-4, C-5), 109.7, 112.5 (2×s, 2×$\underline{C}$(CH$_3$)$_2$), 170.2 (s, C-1); *m*/*z* (APCI+ve): 316 ($M-N_2+H^+$, 100%).

5.7. Isopropyl 6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonyl)-amino-D-allonate (dimer) 3

Aqueous sodium hydroxide (1 ml, 1 M) was added to a stirred solution of the methyl ester **2** (260 mg, 0.83 mmol) in dioxane (4 ml). The reaction mixture was stirred under nitrogen for 16 h at room temperature. TLC (ethyl acetate:hexane 1:6) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.0). The solvent was removed in vacuo and the residue dissolved in water (2 ml) and stirred with Amberlite IR-120(H^+) resin for 1 min. The resin was removed by filtration and the solvent removed in vacuo to yield crude 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonic acid **14**, used without further purification.

A solution of the isopropyl ester **15** (250 mg, 0.73 mmol) in isopropyl alcohol was stirred under an atmosphere of hydrogen in the presence of palladium black (15 mg). After 6 h, TLC (ethyl acetate:hexane 1:4) indicated complete conversion of the starting material (R_f 0.7) to a major product (R_f 0.0). The reaction mixture was filtered through Celite eluting with isopropyl alcohol and the solvent removed in vacuo to yield isopropyl amine **16**, used without further purification.

1-(3-Dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (239 mg, 1.24 mmol) was added to a stirred solution of the acid **14**, 1-hydroxybenzotriazole (HOBt) (170 mg, 1.24 mmol) and diisopropylethylamine (0.22 ml, 1.24 mmol) in dichloromethane (2 ml) at 0°C. The mixture was stirred for 30 min, then a solution of the crude amine **16** in dichloromethane (1.5 ml) added. The reaction mixture was stirred at room temperature for 17 h. TLC (ethyl acetate:hexane 1:1) indicated conversion of the starting materials to a major product (R_f 0.5). The reaction mixture was diluted with dichloromethane (25 ml) and washed with dilute hydrochloric acid (2 M, 15 ml) and pH 7 buffer (15 ml). The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate:hexane 1:2) to yield the dimer **3** (256 mg, 58%) as an amorphous white solid; (HRMS: $M+H^+$: 601.308484. $C_{27}H_{45}N_4O_{11}$ requires: 601.308455); $[\alpha]_D^{25}=+19.2$ (*c* 0.6 in $CHCl_3$); ν_{max}(thin film): 2101 (N_3), 1742 (b, C=O ester, amide I), 1686 (amide II), cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.27, 1.29 (2×3H, 2×d, $J_{vicinal}$ 2.7 Hz, OCH(C$\underline{H}_3$)$_2$), 1.31, 1.35, 1.36, 1.39, 1.44, 1.48, 1.50, 1.52 (8×3H, 8×s, 4×C(C$\underline{H}_3$)$_2$), 3.44 (1H, dd, $J_{6,6'}$ 12.9 Hz, $J_{6,5}$ 3.6 Hz, H-6^A), 3.51 (2H, m, H-6′^{A}, H-6^B), 3.77 (1H, a-quin, J_{app} 6.8 Hz, H-6′^{B}), 4.01 (1H, dd, $J_{4,3}$ 9.4 Hz, $J_{4,5}$ 5.4 Hz, H-4^B), 4.17 (1H, dd, $J_{4,3}$ 9.3 Hz, $J_{4,5}$ 5.8 Hz, H-4^A), 4.30 (2H, m, H-5^A, H-5^B), 4.40 (3H, m, H-2^B, H-3^A, H-3^B), 4.61 (1H, d, $J_{2,3}$ 6.2 Hz, H-2^A), 5.07 (1H, septet, *J* 6.3 Hz, OC$\underline{H}$(CH$_3$)$_2$), 6.84 (1H, t, $J_{6',NH}$ 6.1 Hz, NH); δ_C (100.6 MHz, $CDCl_3$): 21.6 (2×q, OCH($\underline{C}H_3$)$_2$), 25.2, 25.5, 25.6, 26.1, 27.5, 27.5, 27.6, 28.0 (8×q, 4×C($\underline{C}H_3$)$_2$), 37.8 (t, C-6^B), 50.9 (t, C-6^A), 69.3 (d, O$\underline{C}$H(CH$_3$)$_2$), 74.1, 75.1, 75.2, 76.2, 77.0, 77.3, 78.0, 78.7 (8×d, C-2^A, C-3^A, C-4^A, C-5^A, C-2^B, C-3^B, C-4^B, C-5^B), 109.2, 109.7, 110.1, 112.3 (4×s, 4×C(CH$_3$)$_2$), 167.3, 170.1 (2×s, C-1^A, C-1^B); *m*/*z* (APCI+ve): 601 (MH^+, 100%), 623 (MNa^+, 65%).

5.8. Isopropyl 6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonate (tetramer) 4

Aqueous sodium hydroxide (0.11 ml, 1 M) was added to a stirred solution of the dimer **3** (57 mg, 0.095 mmol) in dioxane (1 ml). The reaction mixture was stirred under nitrogen for 24 h at room temperature. TLC (ethyl acetate:hexane 1:2) 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, the residue dissolved in water (1 ml) and stirred with Amberlite IR-120(H^+) resin for 1 min. The resin was removed by filtration and the solvent removed in vacuo to yield the crude dimer acid acid **17**, used without further purification.

A solution of the dimer **3** (51 mg, 0.085 mmol) in isopropyl alcohol (2 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (5 mg). After 24 h, TLC (ethyl acetate:hexane 1:2) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.0). The reaction mixture was filtered through Celite, and the solvent removed in vacuo to yield the crude dimer amine **18**, used without further purification.

EDCI (29 mg, 0.15 mmol) was added to a stirred solution of the dimer acid **17**, HOBt (20 mg, 0.15 mmol) and diisopropylethylamine (0.026 ml, 0.15 mmol) in dichloromethane (0.5 ml) at 0°C. The mixture was stirred for 30 min, then a solution of the dimer amine **3** in dichloromethane (0.5 ml) added. The reaction mixture was stirred at room temperature for 17 h. TLC (ethyl acetate:hexane 3:2) indicated conversion of the starting materials to a major product (R_f 0.15). The reaction mixture was diluted with dichloromethane (10 ml) and washed with dilute hydrochloric acid (2 M, 8 ml) and pH 7 buffer (8 ml). The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate:hexane 1:2) to yield the tetramer **4** (50 mg, 53%) as an amorphous solid; *m/z* (ES+ve), (MeCN:H_2O, 1:1; CV = +50 V): 1137.54 ($M+Na^+$; 100%), 1138.54 (60%), 1139.50 (20%), 1140.50 (4%). $[C_{51}H_{82}N_6O_{21}Na]^+$ requires: 1137.54 ($M+Na^+$; 100%), 1138.55 (60%), 1139.55 (20%), 1140.50 (4%). $[\alpha]_D^{25} = +25.9$ (*c* 0.8 in $CHCl_3$); ν_{max}(thin film): 2102 (N_3), 1743 (b, C=O ester), 1688 (amide), cm^{-1}; δ_C (100.6 MHz, $CDCl_3$): 21.6, 21.8 (2×q, $OCH(\underline{C}H_3)_2$), 25.2, 25.4, 25.5, 25.6, 25.6, 26.1, 26.4 (8×q, $4\times C(\underline{C}H_3)_2$), 27.4, 27.6, 27.6, 27.7, 27.8, 28.0, 28.1, (8×q, $4\times C(\underline{C}H_3)_2$), 37.7, 38.1, 38.5 (3×t, C-6^B, C-6^C, C-6^D), 50.9 (t, C-6^A), 69.3 (d, $CO_2\underline{C}H(CH_3)_2$), 74.1, 74.4, 74.9, 75.0, 75.0, 75.1, 75.4, 76.0, 76.2, 77.0, 77.2, 77.3, 77.4, 78.0, 78.0, 78.8 (16×d, C-2^A, -3^A, -4^A, -5^A, -2^B, -3^B, -4^B, -5^B, -2^C, -3^C, -4^C, -5^C, -2^D, -3^D, -4^D, -5^D), 109.1, 109.2, 109.3, 109.7, 110.1, 110.2, 111.9, 112.2 (8×s, $8\times\underline{C}(CH_3)_2$), 167.0, 167.3, 170.1, 170.7 (4×s, C-1^A, -1^B, -1^C, -1^D); δ_H (400 MHz, $CDCl_3$): 1.28–1.55 (54H, m, $8\times C(CH_3)_2$, $OCH(C\underline{H}_3)_2$), $8\times C(C\underline{H}_3)_2$), 5.07 (1H, sept, *J* 6.3 Hz, $CO_2C\underline{H}(CH_3)_2$).

Unit	NH	H-2	H-3	H-4	H-5	H-6/H-6′
A	-	4.61	4.41	4.19	4.29	3.44, 3.51
B, C or D	6.84 6.83	or4.39	4.39	4.00	4.33	3.80, 3.48
B, C or D	6.90	4.63	4.35	4.08	4.19	3.76, 3.40
B, C or D	6.84 6.83	or4.48	4.48	4.03	4.31	3.63, 3.63

5.9. Isopropyl 6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonate (hexamer) 5

Aqueous sodium hydroxide (0.1 ml, 1 M) was added to a stirred solution of the dimer **3** (41 mg, 0.068 mmol) in dioxane (1 ml). The reaction mixture was stirred under nitrogen for 24 h at room temperature. 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, the residue dissolved in water (1 ml) and stirred with Amberlite IR-120(H^+) resin for 1 min. The resin was removed by filtration and the solvent removed in vacuo to yield the crude dimer acid, used without further purification.

A solution of the tetramer **4** (76 mg, 0.07 mmol) in isopropyl alcohol (2 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (5 mg). After 24 h, TLC (ethyl acetate:hexane 3:2) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.0). The reaction mixture was filtered through Celite, and the solvent removed in vacuo to yield the tetramer amine, used without further purification.

EDCI (20 mg, 0.10 mmol) was added to a stirred solution of the crude dimer acid, **17** HOBt (14 mg, 0.10 mmol) and diisopropylethylamine (0.018 ml, 0.10 mmol) in dichloromethane (0.5 ml) at 0°C. The mixture was stirred for 30 min, then a solution of the crude tetramer amine in dichloromethane (0.5 ml) added. The reaction mixture was stirred at room temperature for 17 h. TLC (ethyl acetate:hexane 3:1) indicated conversion of the starting materials to a major product (R_f 0.2). The reaction mixture was diluted with dichloromethane (10 ml) and washed with dilute hydrochloric acid (2 M, 8 ml) and pH 7 buffer (8 ml). The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate:hexane 3:1) to yield the hexamer **5** (50 mg, 45%) as an amorphous solid; *m/z* (ES+ve), (MeCN:H_2O, 1:1; CV = +70 V): 1651.85 ($M+Na^+$; 100%), 1652.85 (87%), 1653.85 (40%), 1654.84 (15%), 1655.83 (3%). $[C_{75}H_{120}N_8O_{31}Na]^+$ requires: 1651.80 ($M+Na^+$; 100%), 1652.80 (87%), 1653.80 (40%), 1654.80 (15%), 1655.83 (3%); $[\alpha]_D^{25} = +34.5$ (*c* 0.65 in $CHCl_3$); ν_{max}(thin film): 2103 (N_3), 1739 (b, C=O ester), 1682 (amide), cm^{-1}; δ_C (100.6 MHz, $CDCl_3$): 21.6, 21.6 (2×q, $OCH(\underline{C}H_3)_2$), 25.2, 25.4, 25.5, 25.6, 25.6, 25.7, 26.1 26.4 (12×q, $6\times C(\underline{C}H_3)_2$), 27.4, 27.6, 27.6, 27.7, 27.7, 27.8, 28.0, 28.1 (12×q, $6\times C(\underline{C}H_3)_2$), 37.7, 38.1, 38.1 38.5, 38.5 (5×t, C-6^B, C-6^C, C-6^D, C-6^E, C-6^F), 50.9 (t, C-6^A), 69.3 (d, $O\underline{C}H(CH_3)_2$), 74.1, 74.4, 75.0, 75.1, 75.4, 75.9, 76.0, 76.2, 77.0, 77.3, 77.4, 77.5, 78.0, 78.1, 78.1, 78.8 (16×d, C-2^A, -3^A, -4^A, -5^A, -2^B, -3^B, -4^B, -5^B, -2^C, -3^C, -4^C, -5^C, -2^D, -3^D, -4^D, -5^D, -2^E, -3^E, -4^E, -5^E, -2^F, -3^F, -4^F, -5^F), 109.1, 109.2, 109.2, 109.3, 109.7, 110.1, 110.2, 111.9, 111.9, 112.2, (10×s, $12\times\underline{C}(CH_3)_2$), 167.0, 167.1, 167.3,

170.1, 170.7, 170.7 (6×s, C-1^A, -1^B, -1^C, -1^D, -1^E, -1^F); δ_H (400 MHz, $CDCl_3$): 1.25–1.55 (78H, m, $CO_2CH(C\underline{H}_3)_2$), 12×$C(CH_3)_2$), 3.37–3.44 (2H, m), 3.46–3.53 (3H, m), 3.55–3.68 (3H, m), 3.73–3.83 (4H, m), 3.99–4.05 (3H, m), 4.08–4.13 (2H, m), 4.17–4.21 (3H, m), 4.29–4.43 (9H, m), 4.46–4.51 (4H, m), 4.61–4.63 (3H, m), 5.07 (1H, sept, J 6.3 Hz, $CO_2C\underline{H}(CH_3)_2$), 6.81–6.85 (3H, m, 3×NH), 6.90 (2H, m, 2×NH). Only partial assignment of the proton spectrum was possible and is recorded in the table below.

Unit	NH	H-2	H-3	H-4	H-5	H-6/H-6′
A		4.62	4.41	4.19	4.29	3.43, 3.52
	6.83	4.44	4.44	4.00	4.33	3.80, 3.48
	6.89	4.63	4.36	4.10	4.20	3.76, 3.39

Unambiguous assignment of the further three monomer units was impossible due to the significant signal overlap.

5.10. Isopropyl 6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-deoxy-2,3:4,5-di-*O*-isopropylidene-6-*N*-(6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonyl)-amino-D-allonate (octamer) 6

Aqueous sodium hydroxide (0.04 ml, 1 M) was added to a stirred solution of the dimer **3** (17 mg, 0.028 mmol) in dioxane (0.5 ml). The reaction mixture was stirred under nitrogen for 24 h at room temperature. 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, the residue dissolved in water (1 ml) and stirred with Amberlite IR-120(H^+) resin for 1 min. The resin was removed by filtration and the solvent removed in vacuo to yield the crude dimer acid **17**, used without further purification.

A solution of the hexamer **5** (24 mg, 0.015 mmol) in isopropyl alcohol (1 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (5 mg). After 24 h, TLC (ethyl acetate:hexane 3:2) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.0). The reaction mixture was filtered through Celite, and the solvent removed in vacuo to yield the hexamer amine, used without further purification.

EDCI (8 mg, 0.042 mmol) was added to a stirred solution of the crude dimer acid, HOBt (6 mg, 0.042 mmol) and diisopropylethylamine (0.0073 ml, 0.042 mmol) in dichloromethane (0.2 ml) at 0°C. The mixture was stirred for 30 min, then a solution of the crude hexamer amine in dichloromethane (0.2 ml) added. The reaction mixture was stirred at room temperature for 17 h. TLC (ethyl acetate:hexane 3:1) indicated conversion of the starting materials to a major product (R_f 0.1). The reaction mixture was diluted with dichloromethane (10 ml) and washed with dilute hydrochloric acid (2 M, 8 ml) and pH 7 buffer (8 ml). The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate:hexane 3:1) to yield the octamer **6** (41%) as an amorphous solid; m/z (ES+ve), (MeCN:H_2O, 1:1; CV = +30 V): 2161.34 ($M+NH_4^+$; 80%), 2162.29 (100%), 2163.33 (70%), 2164.36 (45%). $[C_{99}H_{158}N_{10}O_{41}Na]^+$ requires: 2161.09 ($M+NH_4^+$; 80%), 2162.10 (100%), 2163.10 (70%), 2164.10 (40%); $[\alpha]_D^{23} = +33.0$ (c 0.37 in $CHCl_3$); ν_{max}(thin film): 2102 (N_3), 1736 (b, C=O ester), 1684 (amide), cm^{-1}; δ_C (100.6 MHz, $CDCl_3$): 21.6, 21.6 (2×q, $CO_2CH(\underline{C}H_3)_2$), 25.2, 25.4, 25.5, 25.6, 25.7, 26.1 26.4 (7×q, 8×$C(\underline{C}H_3)_2$), 27.4, 27.6, 27.6, 27.7, 27.7, 27.8, 27.8, 28.0, 28.1 (9×q, 8×$C(\underline{C}H_3)_2$), 37.7, 38.1, 38.1 38.5, 38.5 (5×t, C-6^B, C-6^C, C-6^D, C-6^E, C-6^F, C-6^G, C-6^H), 50.9 (t, C-6^A), 69.4 (d, $CO_2\underline{C}H(CH_3)_2$), 74.1, 74.4, 75.0, 75.2, 75.4, 75.9, 76.2, 77.0, 77.3, 77.4, 78.1, 78.8 (12×d, C-2^A, -3^A, -4^A, -5^A, -2^B, -3^B, -4^B, -5^B, -2^C, -3^C, -4^C, -5^C, -2^D, -3^D, -4^D, -5^D, -2^E, -3^E, -4^E, -5^E, -2^F, -3^F, -4^F, -5^F, -2^G, -3^G, -4^G, -5^G, -2^H, -3^H, -4^H, -5^H), 109.2, 109.2, 109.3, 109.3, 109.7, 110.1, 110.2, 111.9, 111.9, 112.2, (10×s, 16×$\underline{C}(CH_3)_2$), 167.0, 167.1, 167.3, 170.1, 170.7 (5×s, C-1^A, -1^B, -1^C, -1^D, -1^E, -1^F, -1^G, -1^H); δ_H (400 MHz, $CDCl_3$): 1.24–1.55 (102H, m, $CO_2CH(C\underline{H}_3)_2$), 16×$C(C\underline{H}_3)_2$), 3.35–3.84 (16H, m), 3.99–4.21 (12H, m), 4.27–4.44 (11H, m), 4.46–4.51 (5H, m), 4.61–4.63 (4H, m), 5.07 (1H, sept, J 6.3 Hz, $CO_2C\underline{H}(CH_3)_2$), 6.82–6.86 (4H, m, 4×NH), 6.91 (3H, m, 3×NH). Further assignment of the octamer proton NMR was not possible in view of the complex signal overlap.

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