Journal of Peptide Science
J. Peptide Sci. **11**: 303–318 (2005)
Published online 15 November 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/psc.622

JOURNAL OF PEPTIDE SCIENCE

The synthesis of oligomers of oxetane-based dipeptide isosteres derived from L-rhamnose or D-xylose

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Received 9 August 2004; Accepted 28 August 2004

Abstract: Routes to oligomers (dimers, tetramers, hexamers) of five oxetane-based dipeptide isosteres have been established. Methyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate 'monomer' led, by coupling the corresponding carboxylic acid and amine, to a 'dimer'. Reverse-aldol ring-opening occurred on attempted saponification of the dimer, so all further oligomerization was performed using TBDMS C-3 hydroxyl protection. The silyl protected L-rhamnonate monomer led in turn to the dimer (via the monomer acid and amine), the tetramer (via the dimer acid and amine) and finally the hexamer (via the tetramer acid and dimer amine). In each case the acids were obtained through saponification of the respective methyl esters and the amines were obtained by hydrogenation of the azides; coupling was TBTU-mediated. Essentially the same strategy was employed on equivalent D-lyxonate, 6-deoxy-L-altronate, 6-deoxy-D-gulonate and D-fuconate dipeptide isosteres to give the respective dimers, tetramers and hexamers. Copyright © 2004 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: oxetane; dipeptide isostere; pseudopeptide

INTRODUCTION

The ability of oligopeptide chains to form organized secondary structures in solution is central to the biological roles of peptides and proteins. The tendency to form definite secondary structure, however, is not a unique feature of α-amino-acid assemblies. Short oligomers of carbohydrate-derived tetrahydrofuran dipeptide isosteres, for example, have been shown to adopt regular solution conformations [1]. More recent work has shown that short oligomers of carbohydrate-derived oxetane-based β-amino acids can also adopt regular solution conformations [2]. The results described herein extend this work by reporting the synthesis for conformational studies (which will be presented shortly) of five series of oligomers of type **2** from carbohydrate-derived oxetane-based dipeptide isosteres of type **1** (the synthesis of which has been reported earlier [3]) as generalized in Figure 1.

Initially, it was hoped the dipeptide isosteres could be oligomerized without the need for protection of the hydroxyl group. Previous work [3] had shown that on hydrogenation, the D-lyxonate dipeptide isostere **3** gave a mixture of oligomeric products **5** instead of the desired amino-ester **4** (see Figure 2).

Dimerization of the L-rhamnonate dipeptide isostere **7** was therefore attempted via the more hindered isopropyl ester **8** (generated by transesterification-see Figure 3). This was reduced, again using hydrogen over palladium on carbon (10%), to give the crude amine **9** which was not isolated; no polymerization was observed. The previously non-isolated azido-acid **10** was generated as before from the benzoyl-protected dipeptide isostere intermediate **6** [3]. On this occasion separation of the desired carboxylic acid **10** from the unwanted benzoic acid was achieved by virtue of their differing pK_a values (the pK_a of benzoic acid is 4.2, the pK_a of **10** is unknown, but likely to be below the value of 3.6 for 2-methoxy-acetic acid [4]) Finally, coupling of the crude amino-isopropyl ester **9** to the azido acid **10** was achieved using TBTU and TEA in DMF. This gave, after purification by column chromatography, the desired azido-isopropyl ester dimer **11** in 96% yield from the isopropyl ester **8**, as illustrated in Figure 3.

Although the azido-isopropyl ester dimer **11** had been obtained in good yield from the corresponding monomer **8**, the yield for the formation of **8** from the azido-methyl ester monomer **7** was relatively low. It was speculated that the increased steric hindrance provided by the methyl group at the C-5 position might be sufficient to prevent polymerization occurring on hydrogenation of the azido-methyl ester monomer **7**. For this reason, coupling of the L-rhamnonate dipeptide isostere **7** was attempted without prior conversion to the isopropyl ester. The azide component of this ester was reduced to an amine using hydrogen over palladium on carbon (10%), together with toluenesulphonic acid to trap the amine as an ammonium salt. No polymerization was observed. After filtration through celite, the crude salt was added to the carboxylic acid **10** and the mixture was dissolved in DMF. Coupling of the acid to the amine was again achieved using TBTU and TEA, followed by column chromatography purification to give the desired dimer **13** in 86% yield (see Figure 4).

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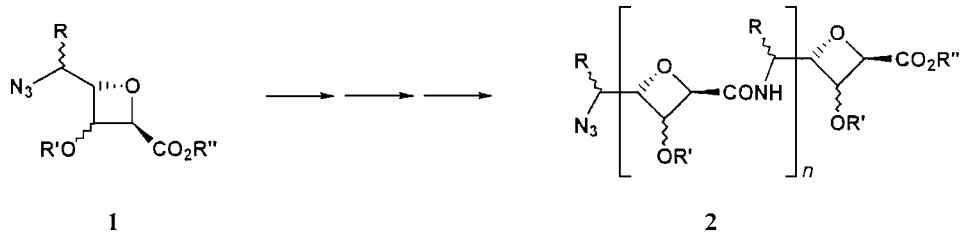

Figure 1 Synthesis of homo-oligomers from dipeptide isostere monomers; R = H or Me, R′ = H or TBDMS, R″ = Me or Pr^i.

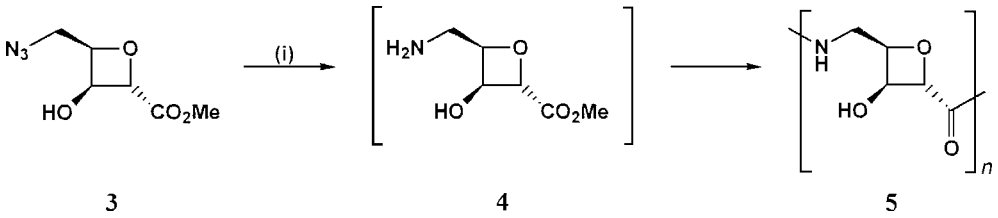

Figure 2 Reduction and *in situ* polymerization of dipeptide isostere **3**. Reagents and conditions; (i) Pd(C), H_2, MeOH.

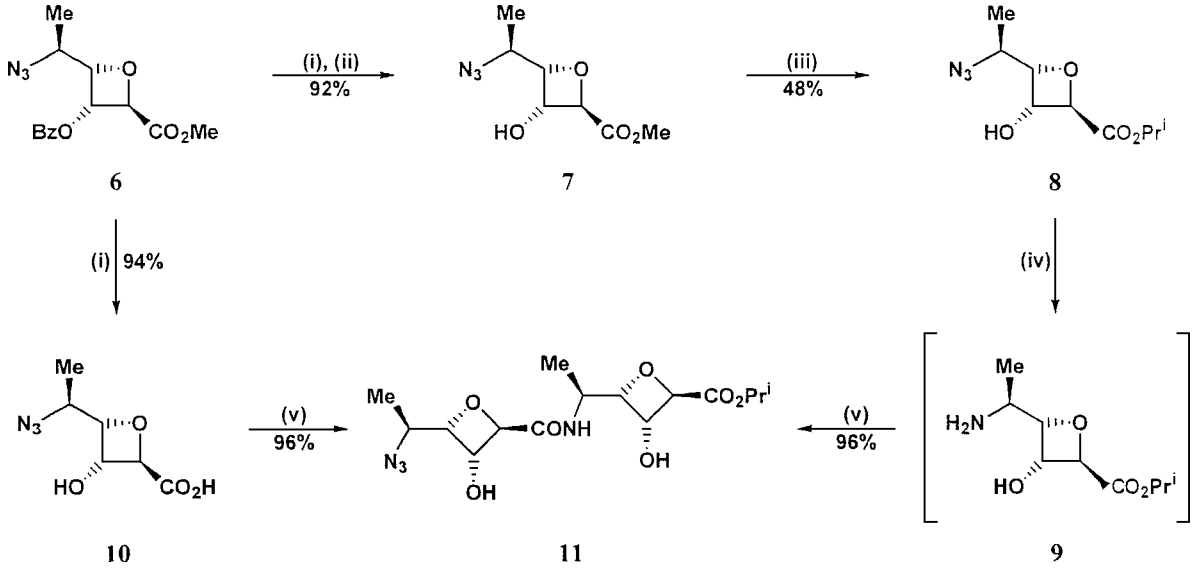

Figure 3 Reagents and conditions; (i) NaOH (4 eq.), THF : H_2O, 7 : 1, RT, 1 day; (ii) MeOH : c.HCl, 100 : 1, RT, 1 day; (iii) Pr^iOH, TsOH (0.03 eq.), 100 °C, 4 days; (iv) Pd(C) 10%, Pr^iOH, H_2, RT, 1.5 days; (v) TBTU (1.2 eq.), TEA (1.4 eq.), DMF, RT, 1 day.

The next stage in the synthesis was to further elaborate the dimer, via coupling to another dimer to give a tetramer. It was envisaged that this tetramer could be obtained by applying essentially the same set of reagents and conditions to the dimer **13** as had been applied to the monomer in order to create the dimer. Accordingly, in order to hydrolyse the methyl ester, the dimer **13** was treated with 1.3 equivalents of potassium carbonate in a 10 : 1 methanol : water solution. Unfortunately, as shown in Figure 5, this led to a mixture of the desired azido-acid dimer **14** and the unwanted side product **15** (arising from a reverse-aldol ring-opening, followed by hydrolysis of the methyl ester and finally intra-molecular hemi-acetal formation). As a result, all further attempts at oligomerization were performed using silyl protection at the C-3 hydroxyl to avoid the reverse-aldol ring-opening. TBDMS protection of the C-3 hydroxyl was chosen as a number of the dipeptide isosteres required the use of this protecting strategy in their synthesis [3]. Further, as a non-UV active group it was also compatible with the later conformational studies by CD spectroscopy.

For the D-lyxonate series, lacking a methyl group at C-5, isopropyl ester protection of the carboxyl terminus was chosen for the reasons outlined above. An iterative strategy to create sequentially the dimer **19**, tetramer **22** and hexamer **24** was chosen for the homo-oligomerization, as outlined in Figure 6. The crude amine **18** was accessed by the hydrogenation of the azido-ester monomer **16** and the crude acid **17**

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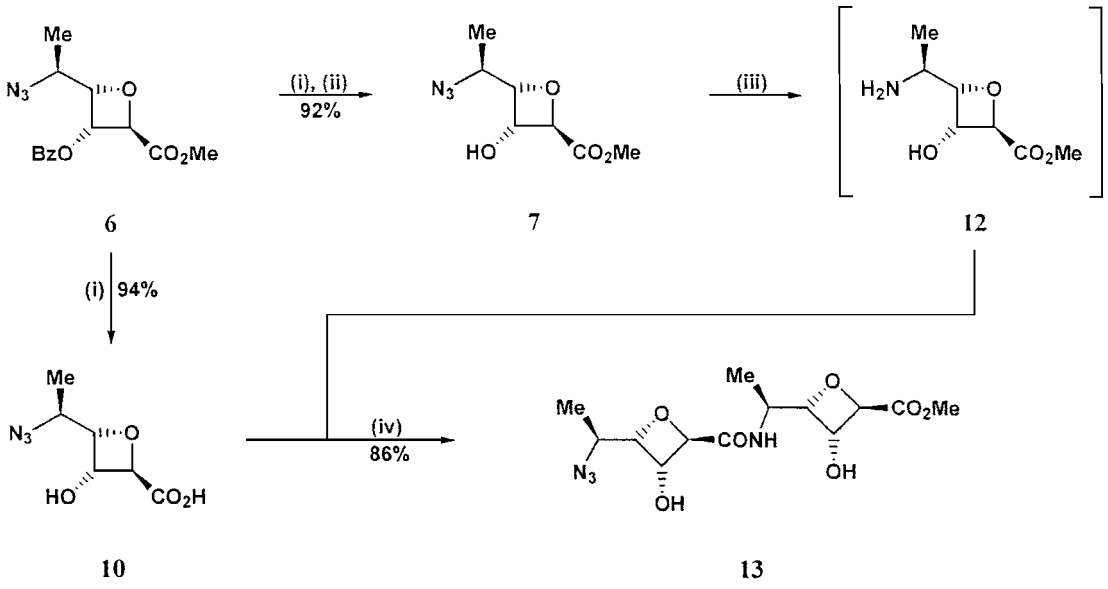

Figure 4 Reagents and conditions; (i) NaOH (4 eq.), THF : H_2O, 7 : 1, RT, 1 day; (ii) MeOH : c.HCl, 100 : 1, RT, 1 day; (iii) TsOH (1.0 eq.), Pd(C) 10%, MeOH, H_2, RT, 1 h; (iv) TBTU (1.2 eq.), TEA (2.4 eq.), DMF, RT, 1 day.

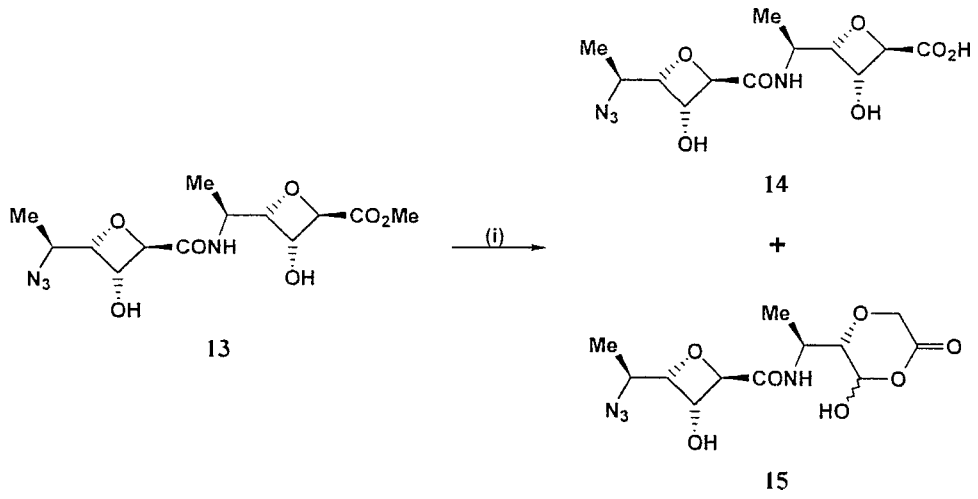

Figure 5 Attempted hydrolysis of dimer **13**. Product ratio **14 : 15**; 3 : 2. Reagents and conditions; (i) K_2CO_3 (1.3 eq.), MeOH : H_2O, 10 : 1, RT, 4 days.

was obtained by saponification of the isopropyl ester **16** with sodium hydroxide followed by acidification of the reaction mixture with amberlite resin (IR 120 H^+ form). On acidification, the pH had to be kept above 4 in order to prevent deprotection of the TBDMS group. The two components were then coupled to give the silyl protected dimer **19** (50% yield over three steps). Essentially the same procedure performed on the azido-ester dimer **19** gave rise to the crude amino-ester dimer **21** and the crude azido-acid dimer **20**, which were then coupled to give the azido-ester tetramer **22** (39% yield over three steps). This in turn led, via the crude azido-acid **23** to the azido-ester hexamer **24** (28% yield over three steps). The reduction in yield for the coupling with increasing length of oligomer was probably due to the loss of silyl protecting groups during either the hydrolysis workup or the final purification on silica.

Essentially the same strategy was adopted for the synthesis of the L-rhamnonate oligomers **28** to **33** (see Figure 7) as was used for the D-lyxonate oligomers. Due to the presence of a methyl group at C-5, however, the methyl ester protection of the carboxyl terminus was retained. Notable differences included the use of potassium carbonate in a 10 : 1 methanol : water solution for the saponification steps, and the use of palladium black in methanol for the hydrogenation steps. The azido-acid monomer **26**, dimer **29** and tetramer **32** were all isolated cleanly and in good yield with no side-reactions being observed. For the coupling steps, a marked improvement in yield over the D-lyxonate series was observed (70% over three steps

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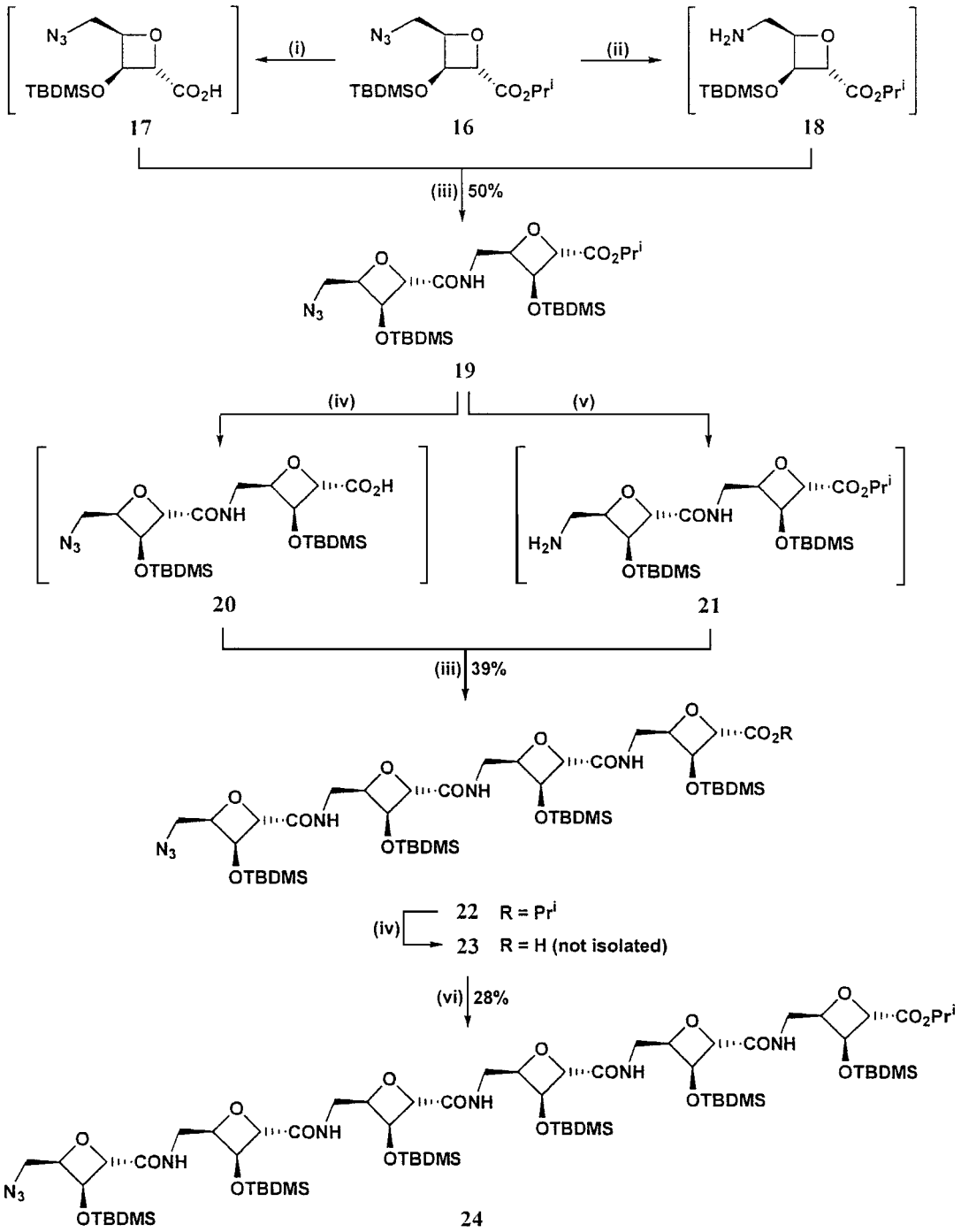

Figure 6 Reagents and conditions; (i) 1 M NaOH (1.1 eq.), THF : H_2O, 6 : 1, RT, 2 h; (ii) Pd(C) 10%, Pr^iOH, H_2, RT, 2 h; (iii) TBTU (1.2 eq.), TEA (1.4 eq.), DMF, RT, 1 day; (iv) K_2CO_3 (1.3 eq.), MeOH : H_2O, 10 : 1, RT, 1 day; (v) Pd(C) 10%, Pr^iOH, H_2, RT, 1 day; (vi) **21** (1.0 eq.), TBTU (1.2 eq.), TEA (1.4 eq.), DMF, RT, 1 day.

for the azido-ester dimer **28**, 84% over three steps for the azido-ester tetramer **31** and 80% yield over three steps for the azido-ester hexamer **33**).

Following the successful oligomerization of the above two series, it was hoped that the equivalent strategy could be employed for the 6-deoxy-L-altronate series. Consequently the azido-ester dimer **37** was obtained in 74% yield over three steps from the azido-ester monomer **34** as outlined in Figure 8.

Saponification of the methyl ester of the dimer was required next. As with the previous series, the azido-ester dimer **37** was treated with potassium carbonate in a 10 : 1 methanol : water solution. On this occasion, the reaction (as observed by TLC) was slower; 4 days were required for the starting material to be consumed completely. This was assumed to be a result of the additional steric crowding around the methyl ester due to the 2,3-*cis* configuration. After neutralization, using

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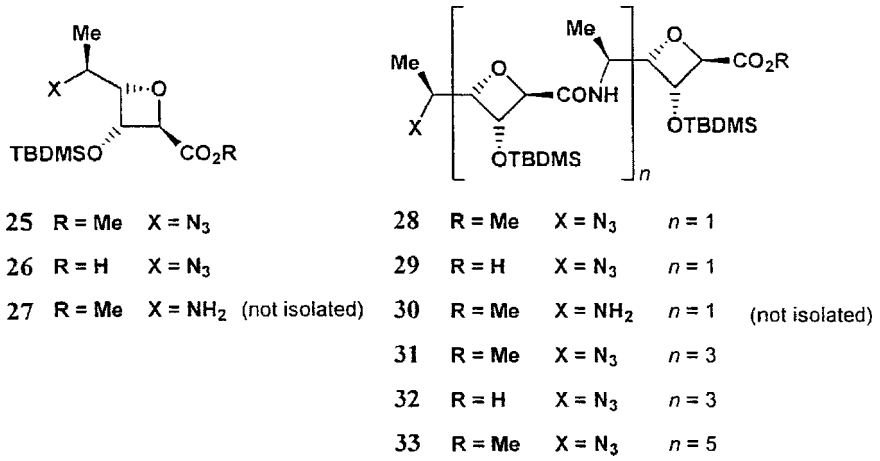

25 R = Me X = N_3
26 R = H X = N_3
27 R = Me X = NH_2 (not isolated)

28 R = Me X = N_3 n = 1
29 R = H X = N_3 n = 1
30 R = Me X = NH_2 n = 1 (not isolated)
31 R = Me X = N_3 n = 3
32 R = H X = N_3 n = 3
33 R = Me X = N_3 n = 5

Figure 7 Silyl-protected L-rhamnonate monomer and oligomers.

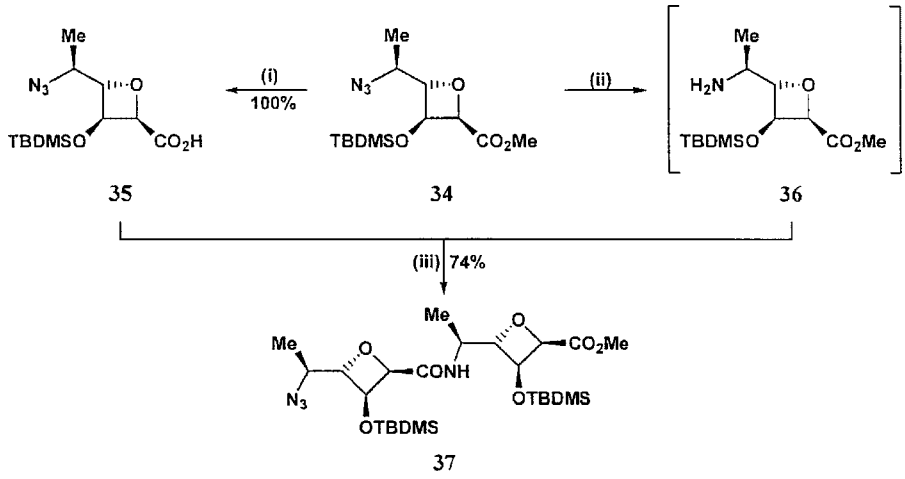

Figure 8 Reagents and conditions; (i) K_2CO_3 (1.3 eq.), MeOH : H_2O, 10 : 1, RT, 1 day; (ii) Pd black, MeOH, H_2, RT, 1 day; (iii) TBTU (1.2 eq.), TEA (1.4 eq.), DMF, RT, 1 day.

Dowex XW(8) resin, the baseline material was revealed by ^{1}H NMR spectroscopy to comprise two closely related products in a 4 : 1 ratio. Separation of the major product was later achieved through a combination of ether/water extractions and column chromatography in CMAH (60 : 30 : 3 : 5). This was shown to be the desired azido-acid **38**, obtained in 37% yield after isolation. It was not possible to isolate the minor product cleanly; analysis did, however, reveal it to be a mono-silyl azido-acid. Comparison with the isolated mono-silyl azido acid **43** (obtained later-see below) showed that it was not the same compound. The minor product from the potassium carbonate hydrolysis was therefore shown (by process of elimination) to be the mono-silyl azido-acid **39** (see Figure 9).

In an attempt to avoid silyl cleavage during hydrolysis, a range of conditions were attempted. All, however, resulted in the formation of a mixture of products. Accordingly, an alternative route to the azido-acid dimer **38** was sought. As the azido-acid monomer **35** had already been successfully synthesized, one possible route was to reduce this to an amino-acid monomer, and couple it to another activated monomer to give the azido-acid dimer **38**. A pentachlorophenyl ester, as first used for peptide synthesis by Kovacs *et al.* [5, 6], was chosen to activate the monomer, allowing isolation of the active ester. The azido-acid monomer **35** was treated with pentachlorophenol and DCCI in DMF. This gave a 3 : 2 ratio of the desired pentachlorophenyl ester **40** and the *N*-acyl urea **41** in a combined yield of 79% as shown in Figure 10. Despite similar polarities, separation did prove possible, allowing access to the pentachlorophenyl ester **40** in yields of up to 50%.

The next requirement en route to the azido-acid dimer **38** was to synthesize the amino-acid monomer **42**. This was performed by treating the azido-acid monomer **35** with palladium black under an atmosphere of hydrogen, as shown in Figure 11. For the coupling, a solution of the crude amino-acid monomer **42** and the pentachlorophenyl ester **40** in DMF was made up in the presence of DIPEA. After 3 days, the solvent was removed, and the residue was dissolved in ether,

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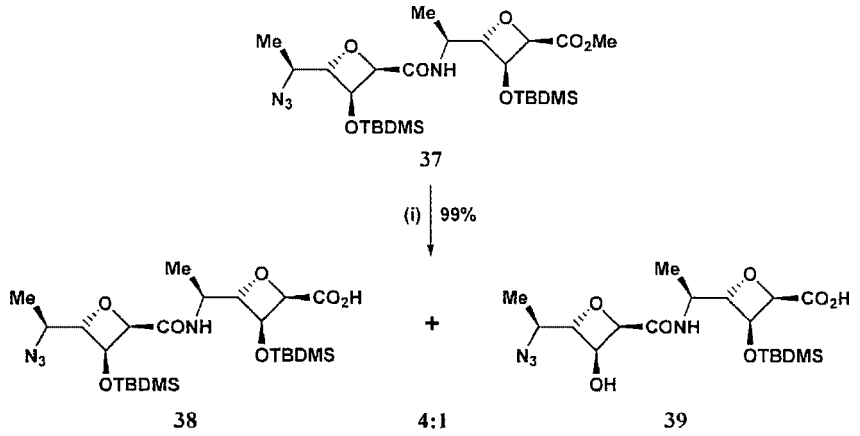

Figure 9 Reagents and conditions; (i) K_2CO_3 (1.3 eq.), MeOH : H_2O, 10 : 1, RT, 4 days.

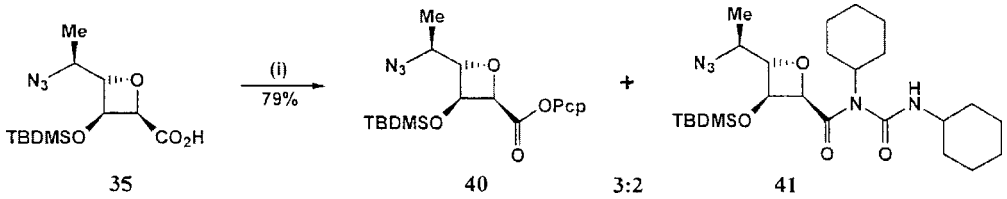

Figure 10 Reagents and conditions; (i) PcpOH (1.0 eq.), DCCI (1.05 eq.), Et_2O, RT, 1 day.

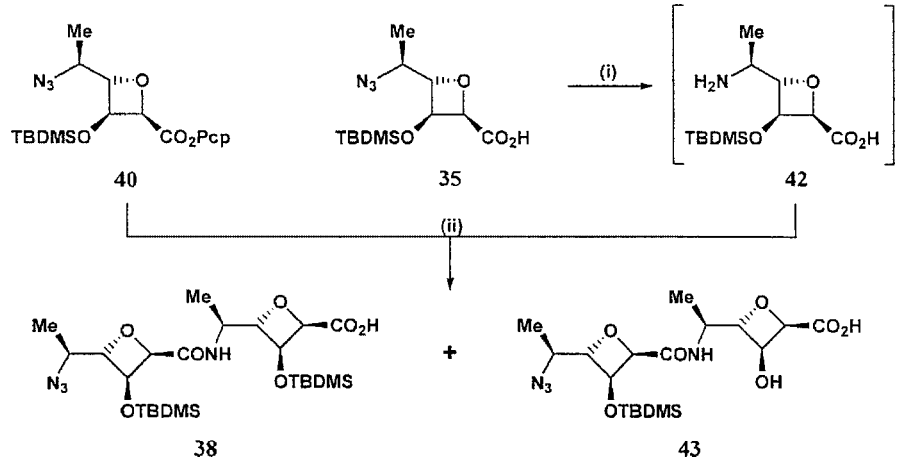

Figure 11 Reagents and conditions; (i) Pd black, MeOH, H_2, RT, 1 day; (ii) DIPEA (1.0 eq.), DMF, RT, 3 days.

and washed with water. Analysis of the organic layer revealed that the coupling reaction had taken place, but that once again there was a mixture of two closely related products. Once again, the major product was shown to be the desired azido-acid dimer **38**. On this occasion, however, it did prove possible to isolate the minor product, subsequently identified as the mono-silyl azido-acid **43**.

Due to the difficulties encountered in isolating the desired azido-acid dimer **38** cleanly in good yield, it was hoped that the mixture obtained from the initial hydrolysis could be utilized without purification to generate a mixture of azido-ester tetramers, from which the fully protected tetramer **45** could be isolated by column chromatography. This would also mean that the strategy that was employed for the earlier series would remain essentially unchanged. Accordingly, reduction of the azido-ester dimer **37** to the amino-ester dimer **44** was carried out using hydrogen over palladium black. Coupling of the crude amino-ester dimer **44** to the azido-acid mixture was again performed using TBTU. In this case, however, the coupling procedure was modified slightly. This was due to the potential for a side-reaction involving the formation of a tetramethylguanidinium derivative, as had been observed on a similar system [7]. The modification involved adding a solution of the azido-acid, TBTU, and the base in DMF to the amino-ester,

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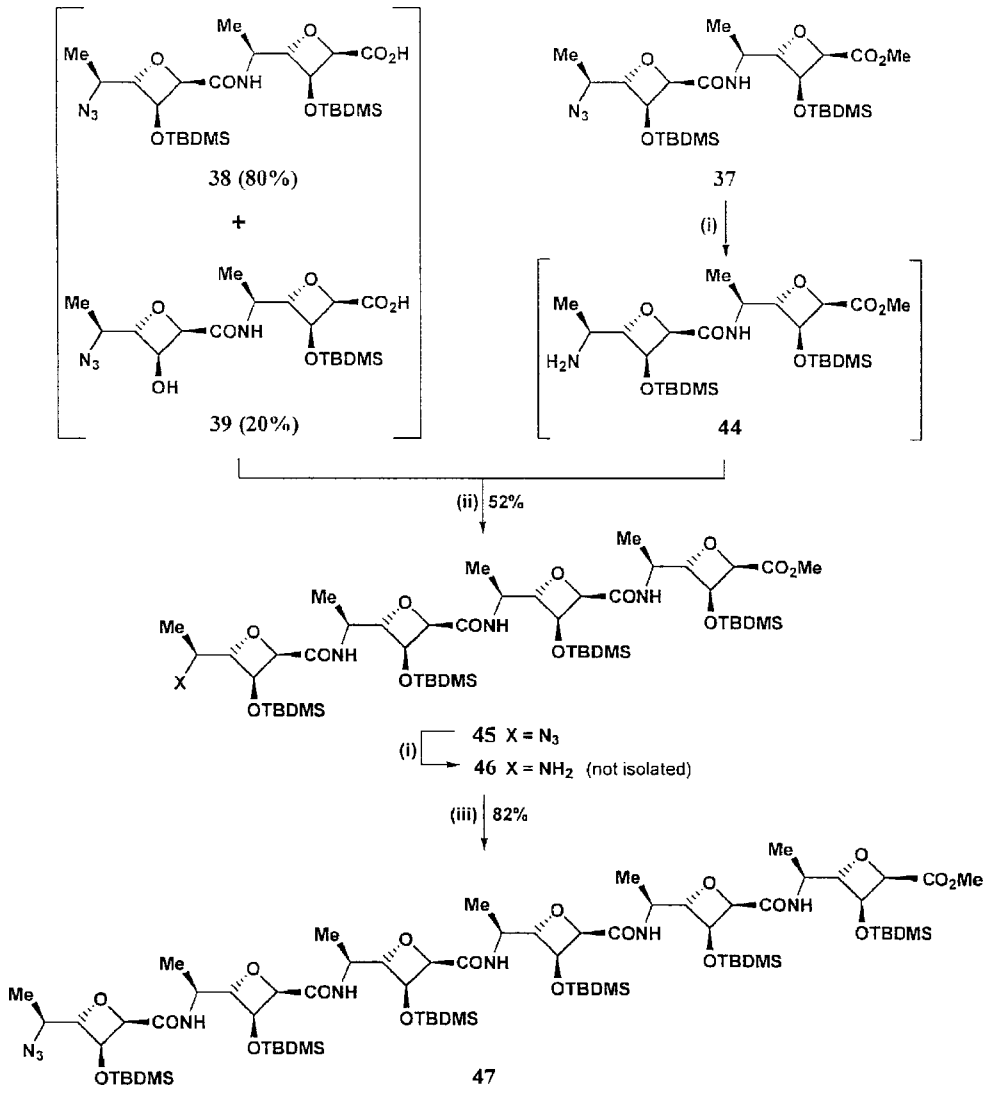

Figure 12 Reagents and conditions; (i) Pd black, MeOH, H_2, RT, 1 day; (ii) TBTU (1.2 eq.), DIPEA (1.05 eq.), DMF, RT, 1 day; (iii) crude **38** (1.0 eq.), TBTU (1.2 eq.), DIPEA (1.05 eq.), DMF, RT, 1 day.

avoiding overexposure of the amine to TBTU. Also, DIPEA was used as a base in place of TEA. Column chromatography then allowed access to the required azido-ester tetramer **45** in 52% yield (see Figure 12), and so despite the mixture generated during the hydrolysis, this strategy remained viable. The relatively low yield of 52% for the coupling was partly due to decomposition of the product on silica. Fortunately, sufficient material had been generated to allow for the synthesis of a hexamer. Avoidance of this problem was therefore not required, although in the very similar D-fuconate series (see Figure 14) Sephadex gel filtration was successfully employed in place of silica. In the previous two series (Figures 6 and 7), the synthesis of the hexamer had been performed by hydrolysis of the azido-ester tetramer to give the azido-acid tetramer, followed by the coupling of this to the crude amino-ester dimer. In light of the saponification problems encountered with the dimer in this series, however, it was thought unwise to follow this route. Instead, the azido-ester tetramer **45** was reduced to the amino-ester tetramer **46** (as outlined in Figure 12). The crude amino-ester tetramer **46** was then coupled to the azido-acid dimer mixture (**38** and **39**). Purification was then achieved via Sephadex gel filtration to give the required fully protected azido-ester hexamer **47** in 82% yield.

The synthesis of the 6-deoxy-D-gulonate oligomers **51** to **56** (See Figure 13) again relied on the overall strategy employed for the previous series. This allowed access to the azido-ester dimer **51** in 78% yield over three steps from the azido-ester monomer **48**. Saponification of the azido-ester dimer **51** gave the required azido-acid dimer **52** in almost quantitative yield. No side-products were observed. The azido-ester tetramer **54** was obtained in 64% yield over three steps via the amino-ester dimer **53** and the azido-acid dimer **52**. The reagents and conditions were identical to those employed for the generation of the 6-deoxy-L-altronate

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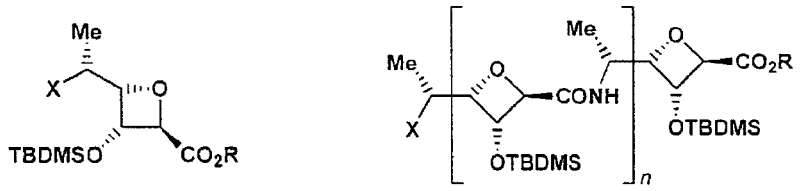
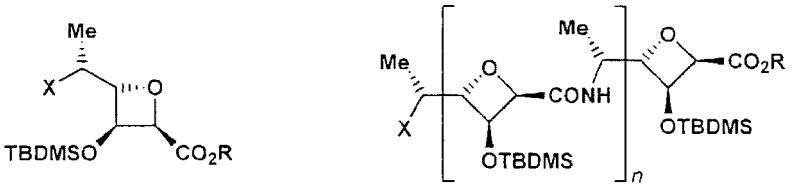


48 R = Me X = N_3
49 R = H X = N_3
50 R = Me X = NH_2 (not isolated)

51 R = Me X = N_3 *n* = 1
52 R = H X = N_3 *n* = 1
53 R = Me X = NH_2 *n* = 1 (not isolated)
54 R = Me X = N_3 *n* = 3
55 R = Me X = NH_2 *n* = 3 (not isolated)
56 R = Me X = N_3 *n* = 5

Figure 13 6-Deoxy-D-gulonate monomer and oligomers.



57 R = Me X = N_3
58 R = H X = N_3
59 R = Me X = NH_2 (not isolated)

60 R = Me X = N_3 *n* = 1
61 R = H X = N_3 *n* = 1
62 R = Me X = NH_2 *n* = 1 (not isolated)
63 R = Me X = N_3 *n* = 3
64 R = Me X = NH_2 *n* = 3 (not isolated)
65 R = Me X = N_3 *n* = 5

Figure 14 D-fuconate monomer and oligomers.

azido-ester tetramer **45**. Almost exact repetition of the above methodology, via the amino-ester tetramer **55** and the azido-acid dimer **52** (previously synthesised en route to the tetramer) then gave the azido-ester hexamer **56** in 62% yield.

The same strategy (i.e. saponification/hydrogenation followed by TBTU coupling) was employed for the synthesis of the D-fuconate dipeptide isostere oligomers **60** to **65** (see Figure 14). As these also possessed a 2,3-*cis* geometry across the oxetane ring, it was thought likely that the deprotection that was encountered during the saponification of the 6-deoxy-L-altronate dimer **37** would again occur. This route would therefore only be viable if the deprotection was minimal in this case. In order to obtain the azido-ester dimer **60**, hydrolysis of the azido-ester monomer **57** to give the azido-acid monomer **58** was performed over 2 days in 98% yield. Only one product was observed. The subsequent reduction and coupling of the azido-ester monomer **57** to give the azido-ester dimer **60** (via the amino-ester monomer **59**) was achieved in 81% yield. The potential problem of hydrolysing the azido-ester dimer **60** was tackled next. As with the monomer, 2 to 3 days were required for the complete consumption of the starting material using potassium carbonate in 10 : 1 methanol : water. Once again, a mixture of products was observed, this time in a 5 : 1 ratio. Separation of these products was attempted using column chromatography in CMAH (60 : 30 : 3 : 5). This led to the isolation of the major product and confirmation that it was the desired silyl-protected azido-acid dimer **61**. Unfortunately, isolation of the minor product did not prove possible, however, the evidence from the analogous 6-deoxy-L-altronate series strongly suggests that this was a mono-silyl derivative. Accordingly, rather than attempt isolation of the azido-acid dimer **61** on each hydrolysis, the crude 5 : 1 mixture was used in the subsequent coupling reaction. Hydrogenation of the azido-ester dimer **60** to the crude amino-ester dimer **62**, followed by TBTU-mediated coupling to the crude azido-acid dimer **61** was performed as before. 2-D TLC indicated that the product was unstable on silica, so it was instead purified by repeated Sephadex gel filtration, to give the azido-ester

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Table 1 % Yields Obtained during Oligomerization of the Silyl-protected Dipeptide Isosteres

OLIGOMERIC SERIES	% YIELD		
	DIMER ($n = 1$), FROM MONOMER	TETRAMER ($n = 3$), FROM DIMER	HEXAMER ($n = 5$), FROM TETRAMER
D-LYXONATE	50%	39%	28%
L-RHAMNONATE	70%	84%	81%
6-DEOXY-L-ALTRONATE	74%	52%	82%
6-DEOXY-D-GULONATE	78%	64%	62%
D-FUCONATE	81%	59%	59%

tetramer **63** in 59% yield over three steps. Repetition of this strategy, via the amino-ester tetramer **64**, led to the azido-ester hexamer **65** in 59% yield.

The work outlined above has enabled the oligomerization of five oxetane-based dipeptide isosteres. For the L-rhamnonate series, formation of the OH-unprotected dimer **13** proved possible, but further elaboration was problematic. For all five series, however, the silyl-protected dimers, tetramers and hexamers have been obtained in good yields (Table 1) despite the various obstacles encountered.

EXPERIMENTAL

Exhaustive NMR and IR spectroscopic data were collected for all the compounds described [8, 9], confirming their formulation as pure single isomers of the structures indicated except where stated otherwise.

THF was distilled from sodium benzophenone ketyl or purchased dry from the Aldrich chemical company in Sure-Seal™ bottles capped with Oxford-Caps™. DMF was purchased dry from the Aldrich chemical company in Sure-Seal™ bottles capped with Oxford-Caps™. Hexane refers to the fraction of petroleum ether that boils in the range 60°–80 °C. 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. All other reagents were used as supplied, without prior purification.

Thin layer chromatography (TLC) was performed on aluminium backed sheets coated with 60 F_{254} silica. Sheets were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid, or 0.5% ninhydrin in methanol (for amines). Column chromatography was performed using C60 40/60 silica. Melting points were recorded on a Kofler hot block. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml. Low resolution mass spectra (m/z) were recorded either on a Micromass Platform I mass spectrometer using atmospheric pressure chemical ionization (APCI), or on a Micromass BioQ II-ZS LCT mass spectrometer using electrospray ionization (ESI), or on a micromass Autospec 500 OAT spectrometer using chemical ionization (CI). High resolution mass spectra (HRMS) were recorded on a micromass Autospec 500 OAT spectrometer using chemical ionization (CI), or on a Waters 2790-Micromass LCT mass spectrometer using electrospray ionization (ESI).

Isopropyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate 8

Toluenesulphonic acid (0.002 g) was added to a solution of methyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate **7** (0.173 g, 0.859 mmol) in Pr^iOH (1.65 ml) under N_2. The solution was heated at 80 °C for 3 days. The temperature was then increased to 100 °C, more toluenesulphonic acid (0.002 g) was added, and the reaction mixture was heated for a further day. At this point TLC (EtOAc : hexane 1 : 1) revealed that the formation of a major product (R_F 0.67). Pr^iOH (5 ml) was added to the solution, which was then neutralized with $NaHCO_3$ to pH5, filtered, and the solvent was removed. The residue was purified by column chromatography (EtOAc : hexane, 1 : 2) to give *isopropyl-2,4-anhydro-5-azido-5-deoxy-L-rhamnonate* (0.095 g, 48% yield) as a colourless oil; $[\alpha]_D^{22}$ +65.5 (*c* 0.94 in $CHCl_3$); υ_{max} (NaCl) 3444.4 cm^{-1} (O–H), 2982.2 cm^{-1} (C–H), 2094.5 cm^{-1} (N_3), 1732.1 cm^{-1} (C=O); δ_H ($CDCl_3$, 400 MHz) 1.28, 1.29 (2 × d, 6H, $CHMe_2$, $J_{CH,Me} = 6.4$ Hz), 1.32 (d, 3H, H-6, $J_{5,6} = 6.8$ Hz), 3.49 (d, 1H, -OH, $J_{3,0H} = 8.4$ Hz), 4.09 (dq, 1H, H-5, $J_{4,5} \approx J_{5,6} \approx 6.4$ Hz), 4.57 (dd, 1H, H-4, $J_{3,4} \approx J_{4,5} \approx 6.4$ Hz), 4.81 (m, 1H, H-3), 4.93 (d, 1H, H-2, $J_{2,3} = 5.2$ Hz), 5.13 (sept, 1H, $CHMe_2$, $J_{CH,Me} = 6.4$ Hz); δ_C ($CDCl_3$, 100.6 MHz) 15.09 (C-6), 21.85 ($CHMe_2$), 58.25 (C-5), 69.49 ($CHMe_2$), 70.42 (C-3), 85.91, 86.07 (C-2, C-4), 169.90 (C-1). MS (CI^+) m/z: 247.(MNH_4^+, 100%), 230 (MH^+, 7%); HRMS: MNH_4^+ found 247.140858, $C_9H_{19}N_4O_4^+$ requires 247.140630.

2,4-anhydro-5-azido-5-deoxy-L-rhamnonic acid 10

1M NaOH (2.97 ml, 4.0 eq.) was added dropwise to a solution of methyl 2,4-anhydro-3-*O*-benzoyl-5-azido-5-deoxy-L-rhamnonate **6** (0.226 g, 0.740 mmol) in THF (5.16 ml) and H_2O (0.74 ml) under N_2. The solution was stirred at room temperature for 1 day, at which point TLC (CMAH, 60 : 30 : 3 : 5) indicated the formation of a single non-UV-active product (R_F 0.33). The solvent was removed, and the residue was dissolved in H_2O (25 ml). The solution was acidified with 0.1 M HCl to pH 1–2, and extracted with $CHCl_3$ (3 × 100 ml). The solvent was removed from the aqueous layer, and the solid residue was extracted with $CHCl_3$ and filtered. The solvent was removed

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from the organic filtrate to give *2,4-anhydro-5-azido-5-deoxy-L-rhamnonic acid* **10** (0.130 g, 94% yield) as a white crystalline solid [8]; m.p. 76°–78 °C; $[\alpha]_D^{22}$ +95.4 (*c* 0.92 in $CHCl_3$). Found C, 38.66; H, 4.92; N, 22.53; $C_6H_9N_3O_4$ requires C, 38.51; H, 4.85; N, 22.45%.

Isopropyl 2,4-anhydro-5-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-5-deoxy-L-rhamnonate 11

A solution of isopropyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate **8** (0.061 g, 0.266 mmol) in Pr^iOH (5 ml) was stirred under H_2 in the presence of a catalytic amount of Pd black. After 36 h, TLC (EtOAc : hexane, 1 : 1) indicated the presence of a single ninhydrin-positive product (R_F 0.0) and no starting material. The reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed, and the residue was dissolved in DMF (1 ml). TBTU (0.100 g, 1.2 equiv.) and 2,4-anhydro-5-azido-5-deoxy-L-rhamnonic acid **10** (0.050 g, 0.267 mmol) were added, and the solution was stirred under N_2 for 15 min, at which point TEA (0.051 ml, 1.4 equiv.) was added. After 20 h, TLC (acetone : hexane, 1 : 1) showed the formation of a major product (R_F 0.38). The solvent was removed, and the residue was purified by column chromatography (acetone : hexane, 1 : 1), to give the non-silylated L-rhamnonate azido-isopropyl ester dimer **11** (0.095 g, 96% yield over two steps) as a colourless oil; $[\alpha]_D^{23}$ +57.7 (*c* 0.92 in $CHCl_3$); υ_{max} (NaCl) 3366.4 cm^{-1} (O–H), 2981.5 cm^{-1}, 2937.5 cm^{-1} (C–H), 2096.8 cm^{-1} (N_3), 1731.9 cm^{-1} (C=O), 1655.3 cm^{-1} (amide I), 1537.5 cm^{-1} (amide II); δ_H ($CDCl_3$, 400 MHz) 1.27–1.30 (m, 9H, B-6 and $CH(CH_3)_2$), 1.32 (d, 3H, A-6, $J_{A5,6} = 6.8$ Hz), 4.10 (dq, 1H, A-5, $J_{A4,5} \approx J_{A5,6} \approx 7.0$ Hz), 4.43–4.50 (m, 2H, A-4 and B-5), 4.55 (dd, 1H, B-4, $J_{B3,4} \approx J_{B4,5} \approx 6.6$ Hz), 4.70–4.75 (2 × d, A-2 and B-2, $J_{A2,3} \approx J_{B2,3} \approx 4.2$ Hz), 5.12 (sept, 1H, $CHMe_2$, $J_{CH,Me} = 6.2$ Hz), 6.96 (d, 1H, NH, $J_{B5,NH} = 8.0$ Hz); δ_C ($CDCl_3$, 50.3 MHz) 15.1, 15.6 (A-6, B-6), 21.9 ($CH(CH_3)_2$), 44.2 (B-5), 56.7 (A-5), 69.5 ($CHMe_2$), 69.9 (A-3, B-3), 84.6 (B-2), 86.5, 86.8, 87.0 (A-2, A-4, B-4), 170.4, 172.0 (A-1, B-1). MS ($APCI^+$) *m/z*: 373 (MH^+, 100%); HRMS: MH^+ found 373.171848, $C_{15}H_{25}N_4O_7^+$ requires 373.172325.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-5-deoxy-L-rhamnonate 13

A solution of methyl 2,4-anhydro-5-azido-5-deoxy-L-rhamnonate **7** (0.051 g, 0.254 mmol) and TsOH (0.048 g, 1.0 eq.) in MeOH (2.35 ml) was stirred under H_2 in the presence of 10% Pd(C) (0.003 g). After 1 h, TLC (EtOAc : hexane, 1 : 1) indicated the presence of one product (R_F 0) and no starting material. The reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed, and the residue was dissolved in DMF (1 ml). TBTU (0.094 g, 1.2 eq.) and 2,4-anhydro-5-azido-5-deoxy-L-rhamnonic acid **10** (0.047 g, 0.251 mmol) were added, and the solution was stirred under N_2 for 15 min, at which point TEA (0.082 ml, 2.4 eq.) was added. After 1 day, TLC (EtOAc : hexane, 2 : 1) showed the formation of a major product (R_F 0.19). The solvent was removed, and the residue was purified by column chromatography (EtOAc : hexane, 2 : 1), to give the non-silylated L-rhamnonate azido-methyl ester dimer **13** (0.075g, 86% yield over two steps) as a colourless oil [8]; $[\alpha]_D^{23}$ +53.6 (*c* 0.77 in $CHCl_3$); MS ($APCI^+$) *m/z*: 158.92 (100%), 345.23 (MH^+, 62%); HRMS: MH^+ found 345.1400, $C_{13}H_{20}N_4O_7^+$ requires 345.1410.

2,4-anhydro-5-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-5-deoxy-L-rhamnonic acid 14

5-(S)-(1′-(S)-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-ethyl)-6-hydroxy- (1,4)-dioxan-2-one 15. K_2CO_3 (0.019 g, 1.3 eq.) was added to a stirred solution of the non-silylated L-rhamnonate azido-methyl ester dimer **13** (0.047 g, 0.137 mmol) in MeOH (3 ml) and H_2O (0.3 ml) at room temperature. TLC (CMAH, 60 : 30 : 3 : 5) after 6 h revealed the formation of two products (R_F 0.49 and R_F 0.26), and the absence of starting material. The solvent was removed, and the crude material was purified via column chromatography (CMAH, 60 : 30 : 3 : 5) to give a 1 : 4 mixture of acetic acid and *5-(S)-[1′-(S)-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-ethyl]-6-hydroxy-[1,4]-dioxan-2-one* **15** (R_F 0.49) (0.023 g), and a 2 : 3 mixture of acetic acid and the non-silylated L-rhamnonate azido-acid dimer **14** (R_F 0.26) (0.037 g).

5-(S)-[1′-(S)-(2,4-anhydro-5-azido-5-deoxy-L-rhamnon-amido) -ethyl]-6-hydroxy-[1,4]-dioxan-2-one **15** [8]: ^1H NMR spectroscopy indicated an epimeric mixture of lactones in a 27 : 23 ratio. MS (ESI^-) *m/z*: 329.19 ($[M\text{-}H]^-$, 100%); HRMS: $[M\text{-}H]^-$ found 329.1099, $C_{12}H_{17}N_4O_7^-$ requires 329.1097.

2,4-anhydro-5-deoxy-5-(2,4-anhydro-5-azido-5-deoxy-L-rhamnonamido)-L-rhamnonic acid **14** [8]: $[\alpha]_D^{23}$ +35.6 (*c* 0.32 in H_2O); MS (ESI^-) *m/z*: 329.14 ($[M\text{-}H]^-$, 100%); HRMS: $[M\text{-}H]^-$ found 329.1101, $C_{12}H_{17}N_4O_7^-$ requires 329.1097.

2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonic acid 17

Isopropyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate **16** (0.100 g, 0.300 mmol) was dissolved in THF (0.52 ml) and H_2O (0.09 ml). 1M NaOH (0.33 ml, 1.1 eq.) was added. The reaction mixture was stirred at room temperature for 2 h after which time TLC (EtOAc : hexane, 1 : 4) showed the formation of one major product (R_F 0.0). The reaction mixture was acidified with amberlite resin (H^+ form, IR 120) to pH 4. DCM (1 ml) was added and the mixture was filtered and concentrated under reduced pressure to yield the crude acid (0.087 g, 100% yield) which was used without further purification.

Isopropyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate 19

Isopropyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate **16** (0.100 g, 0.300 mmol) was dissolved in Pr^iOH (6 ml) and 10% Pd(C) (0.010 g) was added. The reaction mixture was flushed with N_2 and then H_2 and stirred at room temperature for 2 h. TLC (EtOAc : hexane, 1 : 4) showed the complete conversion of starting material to one major product (R_F 0.0). The reaction mixture was degassed, flushed with N_2 and then filtered through Celite. The solvent was removed, crude 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonic acid **17** (0.087 g, 0.300 mmol) was added, and the mixture was dissolved in DMF

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(3 ml). TBTU (0.117 g, 1.2 eq.) was added and the solution was stirred for 20 min. TEA (0.06 ml, 0.430 1.4 eq.) was added and the reaction was stirred at room temperature for 18 h. After that time TLC (EtOAc : hexane, 1 : 4) showed the formation of a major product (R_F 0.46). The solvent was removed and the residue was purified by column chromatography to give the D-lyxonate azido-isopropyl ester dimer **19** (0.081 g, 50% yield over 3 steps) as a colourless oil [9]; $[\alpha]_D^{22}$ −12.5 (*c* 1.15 in $CHCl_3$); MS ($APCI^+$) *m/z*: 573 (MH^+, 100%), 590 (MNH_4^+, 5%). Found: C, 52.36; H, 8.47; N, 9.75; $C_{25}H_{48}N_4O_7Si_2$ requires: C, 52.42; H, 8.45; N, 9.78%.

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonic acid 20

The D-lyxonate azido-isopropyl ester **19** (0.080 g, 0.140 mmol) was dissolved in MeOH (2 ml) and H_2O (0.2 ml). K_2CO_3 (0.025 g, 1.3 eq.) was added and the reaction mixture was stirred at room temperature for 18 h after which time TLC (EtOAc : hexane, 1 : 4) showed the formation of one major product (R_F 0.0). The reaction mixture was acidified with Dowex XW(8) resin to pH 5, filtered and the solvent was removed to give the crude acid (0.074 g, 100% yield) which was used without further purification.

Isopropyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate 22

This was prepared using a procedure essentially unchanged from that used to prepare the D-lyxonate azido-isopropyl ester dimer **19** from the respective azido-isopropyl ester monomer **16** and crude azido-acid monomer **17**.

The D-lyxonate azido-isopropyl ester dimer **19** (0.080 g, 0.140 mmol) and the crude azido-acid dimer **20** (0.074 g, 0.140 mmol) were used to give the D-lyxonate azido-isopropyl ester tetramer **22** (0.057 g, 39% yield over 3 steps) as a glassy solid [9] (R_F 0.2, EtOAc : hexane, 1 : 4); $[\alpha]_D^{24}$ −10.9 (*c* 1.24 in $CHCl_3$). Isotope distribution (ESI^+) found 1059.58 (100%), 1060.50 (74%), 1061.50 (42%), 1062.48 (15%), 1063.52 (5%); $C_{47}H_{91}N_6O_{13}Si_4^+$ requires 1059.57 (100%), 1060.57 (76%), 1061.57 (45%), 1062.57 (19%), 1063.57 (7%).

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonic acid 23

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the respective azido-isopropyl ester dimer **19**.

The D-lyxonate azido-isopropyl ester tetramer **22** (0.070 g, 0.066 mmol) was used to give the crude acid [9] **23** (0.065 g, 97% yield, R_F 0.0, EtOAc : hexane, 1 : 4) which was used without further purification.

Isopropyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-lyxonate 24

This was prepared using a procedure essentially unchanged from that used to prepare the D-lyxonate azido-isopropyl ester dimer **19** from the respective azido-isopropyl ester monomer **16** and crude azido-acid monomer **17**.

The D-lyxonate azido-isopropyl ester dimer **19** (0.038 g, 0.066 mmol) and the crude azido-acid tetramer **23** (0.067 g, 0.066 mmol) were used to give the D-lyxonate azido-isopropyl ester hexamer **24** (0.028 g, 28% over three steps) as a glassy solid [9] (R_F 0.06, EtOAc : hexane, 1 : 4); $[\alpha]_D^{26}$ −10.8 (*c* 0.72 in $CHCl_3$). Isotope distribution (ESI^+) found 1545.92 (86%), 1546.90 (100%), 1547.90 (77%), 1548.89 (43%), 1549.85 (19%), 1550.87 (7%); $C_{69}H_{133}N_8O_{19}Si_6^+$ requires 1545.82 (91%), 1546.82 (100%), 1547.83 (77%), 1548.83 (43%), 1549.83 (20%), 1550.83 (7%).

2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonic acid 26

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the azido-isopropyl ester dimer **19**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate **25** (0.161 g, 0.510 mmol) was used to give *2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5-deoxy-L-rhamnonic acid* **26** (0.153 g, 99% yield) as a white crystalline solid [8] (R_F 0, EtOAc); m.p. 74°–77 °C; $[\alpha]_D^{26}$ +56.8 (*c* 0.62 in $CHCl_3$); MS (CI^+) *m/z*: 302.1 (MH^+, 13%), 319.2 (MNH_4^+, 100%).

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate 28

A solution of methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate **25** (0.104 g, 0.330 mmol) in MeOH (2.5 ml) was stirred under H_2 in the presence of Pd black (0.023 g). After 1 day, TLC (EtOAc : hexane, 1 : 1) indicated the presence of one product (R_F 0.16) and a small amount of starting material (R_F 0.68). The reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed, and the residue was dissolved in DMF (1.7 ml). TBTU (0.125 g, 1.2 eq.) and 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonic acid **26** (0.097 g, 0.322 mmol) were added, and the solution was stirred under N_2 for 15 min, at which point TEA (0.045 ml, 1.4 eq.) was added. After 1 day, TLC (EtOAc : hexane, 1 : 1) showed the formation of a major product (R_F 0.59). The solvent was removed, and the residue was purified by column chromatography (EtOAc : hexane, 2 : 3), to give the silyl-protected L-rhamnonate azido-ester dimer **28** (0.132 g, 70% yield over three steps) as a clear oil [8]; $[\alpha]_D^{24}$ +23.0

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(*c* 1.20 in $CHCl_3$); MS (APCI$^+$) *m/z*: 121.81 (100%), 573.34 (MH^+, 46%). Found C, 52.43; H, 8.48; N, 9.76; $C_{25}H_{48}N_4O_7Si_2$ requires C, 52.42; H, 8.45; N, 9.78%.

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonic acid 29

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the azido-isopropyl ester dimer **19**.

The silyl-protected L-rhamnonate azido-ester dimer **28** (0.036 g, 0.063 mmol) was used to give the silyl-protected L-rhamnonate azido-acid dimer **29** (0.034 g, 97% yield) as a clear oil [8] (R_F 0, EtOAc); $[\alpha]_D^{23}$ +15.5 (*c* 0.55 in MeCN); MS (APCI$^+$) *m/z*: 559.26 (MH^+, 100%). HRMS: $[M-H]^-$ found 557.2820, $C_{24}H_{45}N_4O_7Si_2^-$ requires 557.2827.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate 31

This was prepared using a procedure essentially unchanged from that used to prepare the silyl-protected L-rhamnonate azido-ester dimer **28** from the respective azido-ester monomer **25** and azido-acid monomer **26**.

The silyl-protected L-rhamnonate azido-ester dimer **28** (0.100 g, 0.175 mmol) and the azido-acid dimer **29** (0.096 g, 0.172 mmol) were used, with the final purification step consisting of Sephadex gel filtration (LH20 in MeOH), followed by column chromatography (EtOAc : hexane, 1 : 1) to give the L-rhamnonate azido-ester tetramer **31** (0.160 g, 84% yield over three steps) as a clear oil [8] (R_F 0.55 EtOAc : hexane, 1 : 1); $[\alpha]_D^{24}$ +15.6 (*c* 0.91 in $CHCl_3$); MS (APCI$^+$) *m/z*: 121.87 (100%), 1087.69 (MH^+, 23%). Isotope distribution (ESI$^+$) found 1109.63 (100%), 1110.57 (79%), 1111.53 (43%), 1112.56 (19%), 1113.58 (7%); $C_{49}H_{94}N_6O_{13}Si_4^+$ requires 1109.59 (100%), 1110.59 (79%), 1111.59 (47%), 1112.59 (20%), 1113.59 (7%).

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonic acid 32

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the azido-isopropyl ester dimer **19**.

The L-rhamnonate azido-ester tetramer **31** (0.023 g, 0.021 mmol) was used to give the respective azido-acid tetramer **32** (0.022 g, 97% yield) as a clear oil [8] (R_F 0, EtOAc); absence of methyl ester confirmed by ^1H NMR spectroscopy; MS (ESI$^-$) *m/z*: 957.50 ([M-TBDMS]$^-$, 100%).

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonate 33

This was prepared using a procedure essentially unchanged from that used to prepare the silyl-protected L-rhamnonate azido-ester dimer **28** from the respective azido-ester monomer **25** and azido-acid monomer **26**.

The silyl-protected L-rhamnonate azido-ester dimer **28** (0.020 g, 0.035 mmol) and the azido-acid tetramer **32** (0.037 g, 0.034 mmol) were used, with final purification by Sephadex gel filtration (LH20 in MeOH) instead of column chromatography, to give the L-rhamnonate azido-ester hexamer **33** (0.045 g, 80% yield over three steps) as a clear oil [8] (R_F 0.68, EtOAc : hexane, 1 : 1); $[\alpha]_D^{25}$ +7.9 (*c* 1.55 in $CHCl_3$). Isotope distribution (ESI$^+$) found 1624.03 (98%), 1625.04 (100%), 1626.04 (80%), 1627.05 (37%), 1628.06 (17%), 1629.13 (8%); $C_{73}H_{140}N_8O_{19}Si_6Na^+$ requires 1623.87 (85%), 1624.88 (100%), 1625.88 (79%), 1626.88 (47%), 1627.88 (21%), 1628.88 (8%).

2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronic acid 35

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the azido-isopropyl ester dimer **19**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronate **34** (0.100 g, 0.317 mmol) was used to give *2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **35** (0.096 g, 100% yield) as a clear oil [8] (R_F 0, EtOAc : hexane, 1 : 1); $[\alpha]_D^{25}$ −8.3 (*c* 1.27 in $CHCl_3$); MS (CI$^+$) *m/z*: 86.2 (100%), 200.3 (84%), 319.4 (MNH_4^+, 33%). HRMS: MNH_4^+ found 319.1800, $C_{12}H_{27}N_4O_4Si$ requires 319.1802.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronate 37

This was prepared using a procedure essentially unchanged from that used to prepare the silyl-protected L-rhamnonate azido-ester dimer **28** from the respective azido-ester monomer **25** and azido-acid monomer **26**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronate **34** (0.085 g, 0.270 mmol) and the equivalent azido-acid monomer **35** (0.081 g, 0.270 mmol) were used to give the 6-deoxy-L-altronate azido-ester dimer **37** (0.115 g, 74% yield over three steps) as a clear oil [8] (R_F 0.62, EtOAc : hexane, 1 : 1); $[\alpha]_D^{21}$ +19.4 (*c* 0.81 in $CHCl_3$); MS (ESI$^+$) *m/z*: 573.31 (MH^+, 90%), 595.29 (MNa^+, 100%). HRMS: MH^+ found 573.3140, $C_{25}H_{49}N_4O_7Si_2^+$ requires 573.3140. Found C, 52.30; H, 8.39; N, 9.38; $C_{25}H_{48}N_4O_7Si_2$ requires C, 52.42; H, 8.45; N, 9.78%.

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2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronic acid 38

K_2CO_3 (0.018 g, 1.3 eq.) was added to a stirred solution of the 6-deoxy-L-altronate azido-ester dimer **37** (0.055 g, 0.096 mmol) in MeOH (2.3 ml) and H_2O (0.23 ml) at room temperature. After 1 day, TLC (EtOAc : hexane, 1 : 1) revealed the formation of a product (R_F 0). The pH was adjusted to pH4 using Dowex XW(8) resin, the reaction mixture was filtered, and the solvent was removed to give *2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **38** and a mono-silyl product (assumed to be *2,4-anhydro-5-(2,4-anhydro-5-azido-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **39**) as a 4 to 1 mixture (0.051 g, 99% yield) which was used without further purification.

On another occasion, a 4 to 1 mixture (0.032 g, 81% yield) generated *via* an essentially identical procedure was dissolved in Et_2O (10 ml) and washed with H_2O (10 ml). The solvent was removed from the organic fraction, and the residue was purified by column chromatography (CMAH, 60 : 30 : 3 : 5). The solvent was removed from those fractions containing one product by TLC (CMAH, 60 : 30 : 3 : 5; R_F 0.5). The residue was dissolved in a mixture of H_2O (1 ml) and MeOH (2 ml). The pH was adjusted to pH3 using Dowex XW(8) resin, and the mixture was filtered. Finally, the solution was extracted with $CHCl_3$ (10 ml), and the solvent was removed from the organic layer to give *2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **38** (0.015 g, 37% yield) as a clear oil. In addition to this, the solvent was removed from the aqueous layer (from the initial Et_2O/H_2O extraction), and the residue was dissolved in H_2O (1 ml). The pH was adjusted to pH3 using Dowex XW(8) resin, and the mixture was filtered. The solution was extracted with $CHCl_3$ (10 ml), and the solvent was removed from the organic layer to give a mono-silyl product (assumed to be *2,4-anhydro-5-(2,4-anhydro-5-azido-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **39**) (0.003 g, 9% yield); ^{1}H NMR ($CDCl_3$, 200MHz) indicates the presence of only one TBDMS group; MS (ESI^-) *m/z*: 443.29 ([M-H]$^-$, 100%).

*2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldi-methylsilyl-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldi-methylsilyl-5,6-deoxy-L-altronic acid* **38** [8]: $[\alpha]_D^{23}$ +23.8 (*c* 0.61 in $CHCl_3$); MS (ESI^-) *m/z*: 425.16 (100%), 557.30 ([M-H]$^-$, 51%). HRMS: [M-H]$^-$ found 557.2831, $C_{24}H_{45}N_4O_7Si_2^-$ requires 557.2827.

Pentachlorophenyl 2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronate 40

***1*-N-*(2,4-Anhydro-5-azido-3-O-tert-butyldimethylsilyl-5,6-deoxy-L-altronyl)-1,3*-N,N′-*dicyclohexylurea 41*.** A solution of DCCI (0.025 g, 1.05 eq. in 0.3 ml DMF) was added to a solution of 2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronic acid **35** (0.035 g, 0.116 mmol) and pentachlorophenol (0.062 g, 2.0 eq.) in DMF (0.3 ml). The resultant solution was stirred at room temperature under N_2. After 1 day, TLC (EtOAc : hexane, 1 : 1) revealed the formation of two products (R_F 0.72 and 0.62), and the solvent was removed. Et_2O was added to the residue, the solution was filtered, and the solvent was removed. The residue was purified by column chromatography (EtOAc : hexane, 1 : 2) to give *pentachlorophenyl 2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronate* **40** (0.032 g, 50% yield) (R_F 0.72, EtOAc : hexane, 1 : 1) as a clear oil.

In an identical run the residue (0.063 g, revealed by ^{1}H NMR spectroscopy to be a 3 : 2 mixture of **40 : 41** in 79% combined yield) was purified by column chromatography (EtOAc : hexane, 1 : 1) to give, in addition to the desired pentachlorophenyl ester, *1-*N-*(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronyl)-1,3-*N,N′-*dicyclohexylurea* **41** (0.010 g, 10% yield) (R_F 0.62, EtOAc : hexane, 1 : 1) as a clear oil.

*Pentachlorophenyl 2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronate* **40** [8]: $[\alpha]_D^{25}$+2.6 (*c* 1.07 in $CHCl_3$); υ_{max} (NaCl) 2858–2953 cm^{-1} (C-H), 2128cm^{-1} (N_3), 1780 cm^{-1} (C=O); MS (ESI^-) *m/z*: 264.85 ($PcpO^-$, 100%).

*1-*N-*(2,4-Anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronyl)-1,3-*N,N′-*dicyclohexylurea* **41** [8]: $[\alpha]_D^{25}$ + 89.9 (*c* 0.24 in $CHCl_3$); MS (ESI^+) *m/z*: 508.08 (MH^+, 100%); HRMS: MH^+ found 508.3317, $C_{25}H_{46}N_5O_4Si$ requires 508.3319.

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido)-5,6-deoxy-L-altronic acid 43

A solution of 2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronic acid **35** (0.022 g, 0.073 mmol) in MeOH (0.5 ml) was stirred under H_2 in the presence of Pd black (0.005 g). After 1 day, a precipitate was observed. The reaction mixture was degassed and flushed with N_2. H_2O was added dropwise until the precipitate re-dissolved and the reaction mixture was then filtered through Celite. The solvent was removed to give the crude amine (0.019 g, 95% yield). A portion of the residue (0.015 g, 0.054 mmol) was dissolved in DMF (0.2 ml) and pentachlorophenyl 2,4-anhydro-5-azido-3-*O-tert*-butyldimethylsilyl-5,6-deoxy-L-altronate **40** (0.030 g, 0.055 mmol) was added. The solution was stirred under N_2 and DIPEA (0.009 ml, 1.0 equiv.) was added. After 3 days, the solvent was removed and the residue was dissolved in Et_2O (10 ml) and then washed with H_2O (10 ml). The solvent was removed from the organic fraction to give a residue containing *2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronic acid* **38** and *2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronamido)-5,6-deoxy-L-altronic acid* **43** as a 3 : 1 mixture (0.025 g). Half the solvent was removed from the aqueous layer, and the pH was adjusted to pH4 using Dowex XW(8) resin. The mixture was filtered, and the solution was extracted with $CHCl_3$ (20 ml). The solvent was removed from the organic layer, and the residue was dissolved in MeCN (5 ml) and washed with hexane (20 ml). The solvent was removed from the MeCN layer to give *2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O-tert-*butyldimethylsilyl-5,6-deoxy-L-altronamido)-5,6-deoxy-L-altronic acid* **43** (0.005 g, 20% yield) as a clear oil [8]; $[\alpha]_D^{22}$ +22.1 (*c* 0.20 in $CHCl_3$); MS ($APCI^-$) *m/z*: 443.21 ([M-H]$^-$, 100%). HRMS: [M-H]$^-$ found 443.1957, $C_{18}H_{31}N_4O_7Si^-$ requires 443.1962.

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Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronate 45

A solution of the 6-deoxy-L-altronate azido-ester dimer **37** (0.017 g, 0.030 mmol) in MeOH (0.5 ml) was stirred under H_2 in the presence of Pd black (0.004 g). After 1 day, TLC (EtOAc : hexane, 1 : 1) indicated the presence of a major product (R_F 0) and a small amount of starting material (R_F 0.6). The reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed to give the crude amine (0.016 g). A solution of TBTU (0.011 g, 1.2 eq.), DIPEA (0.0053 ml, 1.05 eq.) and the crude 6-deoxy-L-altronate azido-acid dimer **38** (0.016 g, 0.030 mmol) in DMF (0.7 ml) was added. The solution was stirred under N_2 for 1 day, at which point TLC (EtOAc : hexane, 1 : 1) showed the formation of a major product (R_F 0.31). The solvent was removed, and the residue was purified by column chromatography (EtOAc : hexane, 2 : 3) to give the 6-deoxy-L-altronate azido-ester tetramer **45** (0.017 g, 52% yield over three steps) as a clear oil [8]; $[\alpha]_D^{27}$ +23.4 (*c* 0.54 in $CHCl_3$). Isotope distribution (ESI^+) found 1104.9 (100%), 1105.9 (63%), 1106.9 (28%), 1107.9 (9%), 1108.9 (3%); $C_{49}H_{98}N_7O_{13}Si_4^+$ requires 1104.6 (100%), 1105.6 (78%), 1106.6 (47%), 1107.6 (19%), 1108.6 (6%).

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-L-altronate 47

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

The 6-deoxy-L-altronate azido-ester tetramer **45** (0.023 g, 0.021 mmol) and the crude azido-acid dimer **38** (0.012 g, 0.022 mmol) were used, with final purification by Sephadex gel filtration (LH20 in MeOH) instead of column chromatography, to give the 6-deoxy-L-altronate azido-ester hexamer **47** (0.029 g, 82% yield over three steps) as a clear oil [8] (R_F 0.41, EtOAc : hexane, 1 : 1); $[\alpha]_D^{22}$ +17.9 (*c* 0.98 in $CHCl_3$). Isotope distribution (ESI^+) found 1618.92 (86%), 1619.92 (100%), 1620.92 (79%), 1621.93 (42%), 1622.93 (21%); $C_{73}H_{140}N_8O_{19}Si_6.NH_4^+$ requires 1618.92 (85%), 1619.92 (100%), 1620.92 (78%), 1621.92 (43%), 1622.92 (21%).

2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonic acid 49

This was prepared using a procedure essentially unchanged to that used to generate the D-lyxonate azido-acid dimer **20** from the azido-isopropyl ester dimer **19**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate **48** (0.088 g, 0.279 mmol) was used to give *2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5,6-deoxy-D-gulonic acid* **49** (0.082 g, 97% yield) as a white crystalline solid [8] (R_F 0, EtOAc : hexane, 1 : 2); m.p. 74–77 °C; $[\alpha]_D^{25}$ +22.8 (*c* 1.05 in $CHCl_3$); MS (ESI^-) *m/z*: 300.14 ($[M\text{-}H]^-$, 100%). HRMS: $[M\text{-}H]^-$ found 300.1382, $C_{12}H_{22}N_3O_4Si^-$ requires 300.1380. Found C, 47.74; H, 7.64; N, 13.91; $C_{12}H_{23}N_3O_4Si$ requires C, 47.82; H, 7.69; N, 13.94%.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate 51

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate **48** (0.097 g, 0.308 mmol) and the equivalent azido-acid monomer **49** (0.091 g, 0.302 mmol) were used, with final purification by column chromatography (EtOAc : hexane, 1 : 2 instead of 2 : 3), to give the 6-deoxy-D-gulonate azido-ester dimer **51** (0.138 g, 78% yield over three steps) as a clear oil [8] (R_F 0.72, EtOAc : hexane, 1 : 1); $[\alpha]_D^{25}$ +37.8 (*c* 0.94 in $CHCl_3$); MS (ESI^+) *m/z*: 573.34 (MH^+, 58%), 595.32 (MNa^+, 100%). HRMS: MH^+ found 573.3140, $C_{25}H_{49}N_4O_7Si_2$ requires 573.3140.

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonic acid 52

K_2CO_3 (0.016 g, 1.3 eq.) was added to a stirred solution of the 6-deoxy-D-gulonate azido-ester dimer **51** (0.050 g, 0.087 mmol) in MeOH (1.5 ml) and H_2O (0.15 ml) at room temperature. After 1 day, TLC (EtOAc : hexane, 1 : 1) revealed the formation of a product (R_F 0) and the absence of any starting material (R_F 0.72). The pH was adjusted to pH4 using Dowex XW(8) resin, the reaction mixture was filtered, and the solvent was removed. The residue was dissolved in $CHCl_3$ (10 ml) and washed with H_2O (5 ml). The solvent was removed from the $CHCl_3$ fraction to give the 6-deoxy-D-gulonate azido-acid dimer **52** (0.048 g, 98% yield) as a clear oil [8]; $[\alpha]_D^{22}$ +42.3 (*c* 0.97 in $CHCl_3$); MS (ESI^-) *m/z*: 557.29 ($[M\text{-}H]^-$, 100%). HRMS: $[M\text{-}H]^-$ found 557.2827, $C_{24}H_{45}N_4O_7Si_2^-$ requires 557.2827.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate 54

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

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The 6-deoxy-D-gulonate azido-ester dimer **51** (0.025 g, 0.044 mmol) and the equivalent azido-acid dimer **52** (0.023 g, 0.041 mmol) were used, with final purification by column chromatography (EtOAc : hexane, 1 : 2 instead of 2 : 3), to give the 6-deoxy-D-gulonate azido-ester tetramer **54** (0.030 g, 64% yield over three steps) as a clear oil [8] (R_F 0.71, EtOAc : hexane, 1 : 1); $[\alpha]_D^{27}$ +45.4 (*c* 0.85 in $CHCl_3$). Isotope distribution (ESI^+) found 1109.57 (100%), 1110.57 (58%), 1111.64 (35%); $C_{49}H_{94}N_6O_{13}Si_4Na^+$ requires 1109.59 (100%), 1110.59 (79%), 1111.59 (47%).

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonamido)-3-*O*-*tert*-butyldimethylsilyl-5,6-deoxy-D-gulonate 56

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

The 6-deoxy-D-gulonate azido-ester tetramer **54** (0.024 g, 0.022 mmol) and the equivalent azido-acid dimer **52** (0.011 g, 0.020 mmol) were used, with final purification by column chromatography (EtOAc : hexane, 1 : 2 instead of 2 : 3), to give the 6-deoxy-D-gulonate azido-ester hexamer **56** (0.021 g, 62% yield over three steps) as a clear oil [8] (R_F 0.79, EtOAc : hexane, 1 : 1); $[\alpha]_D^{24}$ +63.0 (*c* 0.45 in $CHCl_3$); HRMS: MNa^+ found 1623.8754, $C_{73}H_{140}N_8O_{19}Si_6Na^+$ requires 1623.8748. Isotope distribution (ESI^+) found 1618.92 (85%), 1619.92 (100%), 1620.92 (67%), 1621.92 (33%), 1622.92 (14%); $C_{73}H_{140}N_8O_{19}Si_6.NH_4^+$ requires 1618.92 (85%), 1619.92 (100%), 1620.92 (78%), 1621.92 (43%), 1622.92 (21%).

2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconic acid 58

K_2CO_3 (0.036 g, 1.3 eq.) was added to a stirred solution of methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate **57** (0.064 g, 0.203 mmol) in MeOH (2.71 ml) and H_2O (0.27 ml) at room temperature. After 2 days, TLC (EtOAc : hexane, 1 : 1) revealed the formation of a major product (R_F 0). The solvent was removed, and the residue was dissolved in H_2O (20 ml) and washed with Et_2O (10 ml). The volume of the aqueous layer was reduced *in vacuo* (to approximately 2 ml), and MeOH (2 ml) was added. The pH was adjusted to pH4 using Dowex XW(8) resin, the mixture was filtered, and the solvent was removed to give *2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5-deoxy-D-fuconic acid* **58** (0.060 g, 98% yield) as a clear oil [8]; $[\alpha]_D^{23}$ −21.8 (*c* 0.66 in $CHCl_3$); MS (ESI^-) *m/z*: 299.81 ($[M-H]^-$, 100%). HRMS: $[M-H]^-$ found 300.1389, $C_{12}H_{22}N_3O_4Si^-$ requires 300.1380.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate 60

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

Methyl 2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate **57** (0.025 g, 0.079 mmol) and the equivalent azido-acid monomer **58** (0.024 g, 0.080 mmol) were used, with final purification by column chromatography (EtOAc : hexane, 1 : 2 instead of 2 : 3), to give the D-fuconate azido-ester dimer **60** (0.037 g, 81% yield over three steps) as a white crystalline solid [8] (R_F 0.64, EtOAc : hexane, 1 : 1); m.p. 136–138 °C; $[\alpha]_{365}^{23}$ +34.8 (*c* 1.04 in $CHCl_3$); MS (ESI^+) *m/z*: 573.15 (MH^+, 54%), 595.12 (MNa^+, 100%). HRMS: MH^+ found 573.3152, $C_{25}H_{49}N_4O_7Si_2^+$ requires 573.3140. Found C, 52.49; H, 8.46; N, 9.69; $C_{25}H_{48}N_4O_7Si_2$ requires C, 52.42; H, 8.45; N, 9.78%.

2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconic acid 61

K_2CO_3 (0.007 g, 1.3 eq.) was added to a stirred solution of the D-fuconate azido-ester dimer **60** (0.022 g, 0.038 mmol) in MeOH (0.85 ml) and H_2O (0.085 ml) at room temperature. After 3 days, TLC (EtOAc : hexane, 1 : 1) revealed the formation of a major product (R_F 0). The pH was adjusted to pH4 using Dowex XW(8) resin, the reaction mixture was filtered, and the solvent was removed to give *2,4-anhydro-5-(2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5-deoxy-D-fuconamido)-3*-O-tert-*butyldimethylsilyl-5-deoxy-D-fuconic acid* **61** and a mono-silyl derivative as a 5 to 1 mixture (0.019 g, 93% yield) which was used without further purification.

On another occasion, a 5 to 1 mixture (0.022 g, 92% yield) generated *via* an essentially identical procedure was purified by column chromatography (CMAH, 60 : 30 : 3 : 5) to give *2,4-anhydro-5-(2,4-anhydro-5-azido-3*-O-tert-*butyldimethylsilyl-5-deoxy-D-fuconamido)-3*-O-tert-*butyldimethylsilyl-5-deoxy-D-fuconic acid* **61** (0.010 g, 41% yield) as a clear oil [8]; $[\alpha]_D^{25}$ +9.1 (*c* 0.42 in $CHCl_3$); MS (ESI^-) *m/z*: 425.00 (100%), 557.11 ($[M-H]^-$, 93%). HRMS: $[M-H]^-$ found 557.2802, $C_{24}H_{45}N_4O_7Si_2^-$ requires 557.2827.

Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate 63

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

The D-fuconate azido-ester dimer **60** (0.030 g, 0.052 mmol) and the crude azido-acid dimer **61** (0.027 g, 0.050 mmol) were used, with final purification by repeated Sephadex gel filtration (LH20 in MeOH) instead of column chromatography, to give the D-fuconate azido-ester tetramer **63** (0.034 g, 59% yield over three steps) as a clear oil [8] (R_F 0.48, EtOAc : hexane, 1 : 1); $[\alpha]_D^{26}$ +21.1 (*c* 0.91 in $CHCl_3$). Isotope distribution (ESI^+) found 1104.6 (100%), 1105.6 (59%), 1106.6 (33%), 1107.6 (12%); $C_{49}H_{98}N_7O_{13}Si_4^+$ requires 1104.6 (100%), 1105.6 (78%), 1106.6 (47%), 1107.6 (19%).

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Methyl 2,4-anhydro-5-(2,4-anhydro-5-azido-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(*N* → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido-(N → 5)-2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconamido)-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-D-fuconate 65

This was prepared using a procedure essentially unchanged from that used to prepare the 6-deoxy-L-altronate azido-ester tetramer **45** from the respective azido-ester dimer **37** and crude azido-acid dimer **38**.

The D-fuconate azido-ester tetramer **63** (0.022 g, 0.020 mmol) and the crude azido-acid dimer **61** (0.011 g, 0.020 mmol) were used, with final purification by repeated Sephadex gel filtration (LH20 in MeOH) instead of column chromatography, to give the D-fuconate azido-ester hexamer **65** (0.019 g, 59% yield over three steps) as a yellow oil [8] (R_F 0.48, EtOAc : hexane, 1 : 1); $[\alpha]_D^{25}$ +30.2 (*c* 0.41 in $CHCl_3$). Isotope distribution (ESI^+) found 1623.82 (91%), 1624.77 (100%), 1625.78 (76%), 1626.80 (42%), 1627.82 (23%), 1628.77 (9%); $C_{73}H_{140}N_8O_{19}Si_6.Na^+$ requires 1623.87 (94%), 1624.88 (100%), 1625.88 (79%), 1626.88 (45%), 1627.88 (21%), 1628.88 (9%).

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