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Short Communication

Cyclic oligomers of oxetane-based dipeptide isosteres derived from L-rhamnose

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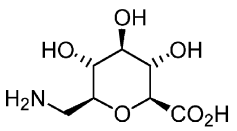
Abstract: Two new cyclic oligomers, cyclo-tetra-[2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-($N\rightarrow5$)] and the corresponding 6-deoxy-D-gulonate cyclic 'tetramer', have been synthesised from linear tetrameric oligomers, using TBTU- and pentafluorophenyl ester–based methodologies, respectively. These two compounds constitute a novel class of cyclic oligomers derived from oxetane-based sugar amino acids. Copyright © 2006 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: cyclic oligomers; oxetane; dipeptide isostere; rhamnose; cyclopeptidomimetics

Over the past decade, the incorporation of sugar amino acids (offering the advantages of precise stereochemical design coupled with conformational restriction and tailored hydrophilicity [1]) into cyclic peptides has become an increasingly active area of research. Kessler *et al.* were the first to demonstrate the potential of such components, when in 1994 they incorporated the dipeptide isostere **1** into a cyclic somatostatin analogue with some retention of biological activity [2]. Cyclic oligomers synthesised from sugar amino acids have also been investigated; this relatively new class has the potential to provide mimics of naturally occurring cyclic peptides and cyclodextrins.



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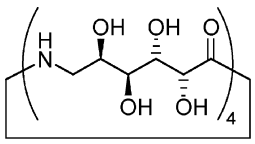

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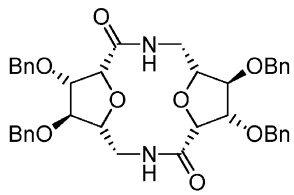

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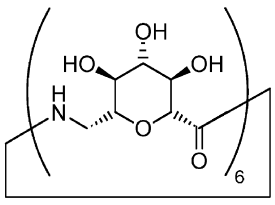

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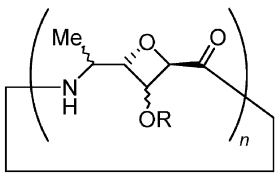

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To date, open-chain [3–5] (e.g. **2**), furanoid [6,7] (e.g. **3**) and pyranoid [7,8] (e.g. **4**) based sugar amino acid cyclic homo-oligomers have been synthesised. Studies on the cyclic 'hexamer' **4** have illustrated its ability to bind *p*-nitrophenol or benzoic acid in a cyclodextrin-like manner [8]. The present work extends these studies to the novel class **5**, with the synthesis of two cyclic compounds incorporating oxetane-based dipeptide isosteres.

Both the new compounds obtained were cyclic tetramers, each synthesised from its respective linear tetramer. The synthesis of the open-chain tetramers from the individual oxetane-based dipeptide isosteres has been outlined previously [9], as also the synthesis of the dipeptide isosteres from L-rhamnose [10]. The first new compound to be obtained was the cyclic L-rhamnonate tetramer **7**. This was synthesised, as shown in Scheme 1, from the azido-acid tetramer **6**. As with the synthesis of the linear oligomers [9], a TBTU-based coupling strategy was employed. Accordingly, the azido-acid tetramer **6** was reduced using hydrogen over palladium black to give the crude amino-acid tetramer. TBTU and Et_3N were then added in DMF solution. The reaction was performed at high dilution (0.2 mM) in order to avoid complications due to polymerisation. Purification by column chromatography after one day then allowed isolation of the desired cyclic L-rhamnonate tetramer **7** in 22% yield over two steps.

For the synthesis of the second cyclic tetramer, an alternative coupling strategy was sought, in an attempt to improve the yield. Complementary studies by a co-worker [3–5], developing routes to open-chain sugar amino acid based cyclic oligomers, had employed

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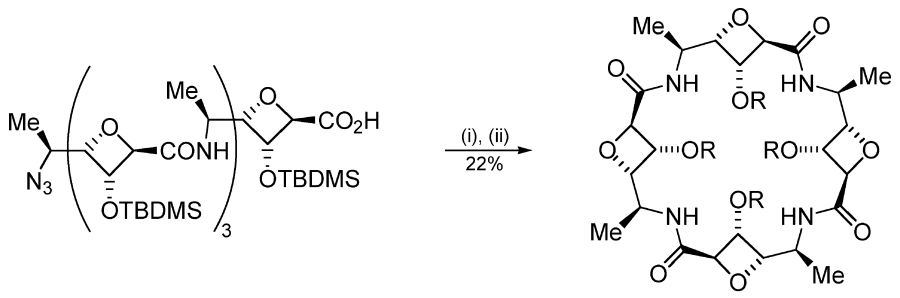


6 7 R = TBDMS

Scheme 1 Reagents and conditions: (i) H_2; Pd black; MeOH; RT; 1 day; (ii) TBTU (1.2 equiv.); Et_3N (1.4 equiv.); DMF; RT; 1 day.

pentafluorophenyl esters to achieve cyclisation in good yield. It was therefore decided to apply the same strategy to the oxetane-based dipeptide isosteres. As the cyclic tetramer **7** based on the L-rhamnonate series had already been synthesised, it was decided, for reasons of diversity, to test the new methodology on the 6-deoxy-D-gulonate series. Accordingly, the azido-methyl ester tetramer **8** was hydrolysed to give the corresponding azido-acid tetramer, which in turn was treated with pentafluorophenol and EDCI in 1,4-dioxane to give the azido-pentafluorophenyl ester **9** in 31% yield over two steps. The relatively low yield is probably a result of unwanted *N*-acyl urea formation; an alternative strategy for the formation of **9**, possibly via a mixed anhydride, should dramatically improve this. It was then envisaged that the azido terminus of **9** could be reduced to an amine, which would react *in situ* to give the cyclic tetramer **10**. Accordingly, the azido-pentafluorophenyl ester tetramer **9** was stirred under hydrogen in the presence of palladium black at high dilution (0.6 mM) in 1,4-dioxane. This gave, after repeated purification by column chromatography, the desired 6-deoxy-D-gulonate cyclic tetramer **10** in 52% yield (see Scheme 2).

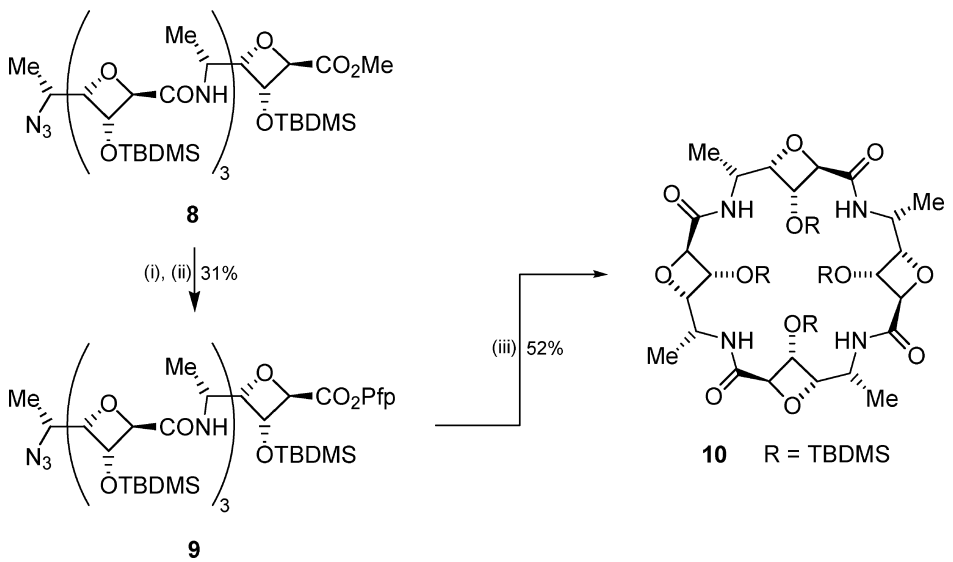
The cyclic tetramers **7** and **10** are the first examples of cyclic oligomers derived from oxetane-based sugar amino acids.

EXPERIMENTAL

The general experimental detail is as reported for the synthesis of the oxetane-based dipeptide isosteres [10].

Cyclo-tetra-(2,4-anhydro-3-*O*-tert-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N*→5)) 7

A solution of the azido-acid tetramer **6** (0.031 g, 0.029 mmol) in MeOH (0.8 ml) was stirred under H_2 in the presence of Pd black (0.008 g). After 22 h the reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed to give the crude amino acid (0.028 g, 92% yield). The residue was dissolved in DMF (130 ml). TBTU (0.014 g, 1.2 equiv.) was added, and the solution was stirred under N_2 for 20 m, at which point Et_3N (0.004 ml, 1.4 equiv.)



Scheme 2 Reagents and conditions: (i) K_2CO_3 (1.3 equiv.); MeOH : H_2O, 10 : 1; RT; 1 day; (ii) PfpOH (2 equiv.); EDCI.HCl (1.2 equiv.); 1,4-dioxane; RT; 1 day; (iii) H_2; Pd black; 1,4-dioxane; RT; 1 day.

was added. After 1 day, TLC (EtOAc) showed the formation of a major product (R_F0.76). The solvent was removed, and the residue was purified by column chromatography (EtOAc) to give cyclo-tetra-[2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-deoxy-L-rhamnonamido-(*N*→5)] **7** (0.007 g, 22% yield) as a clear oil; $[\alpha]_D^{23}$ −7.1 (*c* 0.15 in $CHCl_3$); υ_{max} ($CHCl_3$, 2 mM) 3395 cm^{-1} (N–H), 2858–2961 cm^{-1} (C–H), 1675 cm^{-1} (amide I), 1601 cm^{-1} (amide II); δ_H ($CDCl_3$, 500 MHz) 0.11 (s, 12H, 4 × -Si*Me*), 0.18 (s, 12H, 4 × -Si*Me*), 0.94 (s, 36H, 4 × -Si*Bu*^{t}), 1.49 (d, 12H, 4 × H-6, $J_{5,6} = 6.5$ Hz), 4.34–4.38 (m, 4H, 4 × H-5), 4.69 (dd, 4H, 4 × H-3, $J = 4.5$ Hz, $J' = 6.5$ Hz), 4.73–4.75 (m, 8H, 4 × H-2 and 4 × H-4), 6.74 (d, 4H, 4 × NH, $J_{5,NH} = 8.5$ Hz); δ_C ($CDCl_3$, 125.7 MHz) −5.5, −4.9 (-Si(CH_3)$_2$), 15.2 (C-6), 17.7 (-Si*C*Me$_3$), 25.5 (-SiC(CH_3)$_3$), 45.4 (C-5), 70.2 (C-3), 87.3, 87.5 (C-2 and C-4), 169.0 (C-1); MS (APCI$^+$) *m*/*z*: 121.69 (100%), 1029.77 (MH^+, 2%); Isotope distribution (ESI$^+$) found 1051.61 (100%), 1052.61 (66%), 1053.61 (32%), 1054.54 (17%), 1055.54 (9%); $C_{48}H_{92}N_4O_{12}Si_4Na^+$ requires 1051.57 (100%), 1052.57 (76%), 1053.57 (43%), 1054.57 (19%), 1055.57 (6%).

Cyclo-tetra-(2,4-anhydro-3-*O*-*tert*-butyldimethylsilyl-5-azido-5,6-deoxy-D-gulonamido-(*N*→5)) 10

K_2CO_3 (0.003 g, 1.3 equiv.) was added to a stirred solution of the azido-methyl ester tetramer **8** (0.020 g, 0.018 mmol) in MeOH (0.4 ml) and H_2O (0.04 ml) at room temperature under N_2. After 1 day, TLC (EtOAc : hexane, 1 : 1) revealed the formation of one product (R_F0) and the absence of any starting material (R_F0.67). The pH was adjusted to 4 using Dowex XW(8) resin, the reaction mixture was filtered and the solvent was removed to give the crude acid (0.022 g); absence of methyl ester was confirmed by ^{1}H NMR spectroscopy; MS (ESI-) *m*/*z*: 1071.39 ([M–H]$^-$, 100%).

The crude acid and EDCI.HCl (0.005 g, 1.2 equiv.) were added to a solution of pentafluorophenol (0.007 g, 2.0 equiv.) in 1,4-dioxane (0.3 ml). The solution was stirred at room temperature under Ar for 1 day, after which TLC (EtOAc : hexane, 1 : 1) revealed the formation of a major product (R_F0.79). The solvent was removed and the residue was dissolved in DCM (20 ml), then washed with H_2O (5 ml), followed by aq. $NaHCO_3$ (sat.) (5 ml). The organic fraction was dried ($MgSO_4$) and, filtered and the solvent removed. The residue was purified by column chromatography (EtOAc : hexane, 1 : 2) to give the azido-pentafluorophenyl ester **9** (0.007 g, 31% yield) as a clear oil; υ_{max} (NaCl) 3339 cm^{-1} (N–H), 2859–2955 cm^{-1} (C–H), 2097 cm^{-1} (N_3), 1792 cm^{-1} (C=O), 1675 cm^{-1} (amide I), 1521 cm^{-1} (amide II). A solution of the azido-pentafluorophenyl ester **9** (0.007 g, 0.006 mmol) in 1,4-dioxane (10 ml) was stirred under H_2 in the presence of Pd black (0.004 g). After 3 days, TLC (EtOAc : hexane, 1 : 1) revealed the formation of a major product (R_F0.68). The reaction mixture was degassed, flushed with N_2, and then filtered through Celite. The solvent was removed, and the residue was purified by repeated column chromatography (EtOAc : hexane, 1 : 2) to give cyclo-tetra-[2,4-anhydro-3-*O*-tert-butyldimethylsilyl-5-azido-5,6-deoxy-D-gulonamido-(*N*→5)] **10** (0.003 g, 52% yield) as a clear oil; $[\alpha]_D^{23} + 34.0$ (*c* 0.05 in $CHCl_3$); υ_{max} (NaCl) 3406 cm^{-1} (N–H), 2858–2955 cm^{-1} (C–H), 1688 cm^{-1} (amide I), 1519 cm^{-1} (amide II); δ_H ($CDCl_3$, 500 MHz) 0.11, 0.18 (2 × s, 2 × 12H, 4 × -Si*Me*$_2$), 0.91 (s, 36H, 4 × -Si*Bu*^{t}), 1.21 (d, 12H, 4 × H-6, $J_{5,6} = 6.5$ Hz), 4.43 (dd, 4H, 4 × H-4, $J_{3,4} \approx J_{4,5} \approx$ 6.5 Hz), 4.55–4.59 (m, 4H, 4 × H-5), 4.71 (dd, 4H, 4 × H-3, $J_{2,3} \approx J_{3,4} \approx 5.3$ Hz), 4.75 (d, 4H, 4 × H-2, $J_{2,3} = 5.0$ Hz), 6.75 (d, 4H, 4 × NH, $J_{5,NH} = 7.5$ Hz); δ_C ($CDCl_3$, 125.7 MHz) −5.6, −4.7 (-Si(CH_3)$_2$), 17.6, 17.8 (C-6 and -Si*C*Me$_3$), 25.6 (-SiC(CH_3)$_3$), 43.8 (C-5), 69.2 (C-3), 86.8, 87.4 (C-2 and C-4), 169.7 (C-1); MS (ESI$^+$) *m*/*z*: 187.97 (100%), 229.03 (85%), 412.23 (52%), 1046.02 (MNH_4^+, 35%), 1051.74 (MNa^+, 39%); Isotope distribution (ESI$^+$) found 1046.6 (100%), 1047.6 (59%), 1048.6 (24%), 1049.6 (6%); $C_{48}H_{92}N_4O_{12}Si_4.NH_4^+$ requires 1046.6 (100%), 1047.6 (77%), 1048.6 (44%), 1049.6 (18%).

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