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Mixed sugar–nylon 14-, 28- and 42-membered ring macrocyclic lactams

Benjamin A. Mayes,[a] Andrew R. Cowley,[b] Christopher W. G. Ansell[c] and George W. J. Fleet[a,*]

[a]*Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK*
[b]*Chemical Crystallography Laboratory, Oxford University, 9 Parks Road, Oxford OX1 3QU, UK*
[c]*Smith & Nephew Research Centre, York Science Park, York YO10 5DF, UK*

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Abstract—Hydrogenation of linear ω-azido-pentafluorophenyl esters from mixed oligomers of 6-amino-6-deoxy-D-galactonic acid (or 6-amino-6-deoxy-D-mannonic acid) and 6-aminohexanoic acid gives cyclic peptides containing 14-, 28- and 42-membered ring lactams. Hydrogenation of a tetrameric peptide derived from ε-amino acids gave a 28-membered ring lactam in 79% yield.

1. Introduction

The preceding paper[1] described unsuccessful attempts to prepare fully hydroxylated versions of nylon 6, which instead resulted in the high yield formation of up to 70-membered rings by the cyclisation of oligomers derived from ε-amino acids. Thus the azido-*galactono*-ester **4** was converted into a series of linear homooligomers **1**, which on hydrogenation gave the corresponding macrocyclic lactams **3** in very high yields; such macrocycles may be viewed as members of a novel class of biomaterials, carbopeptoid–cyclodextrins (CPCD), which have structural features common to both macrocyclic carbohydrates and cyclic peptides.

The cyclisation presumably occurs by intramolecular cyclisation of intermediate amino pentafluorophenyl (PFP) esters. Although the cyclisations are efficient for the formation of homooligomers, each of which has the stereochemistry of D-galactonic acid, the full range of structures that gives rise to efficient macrolactamisation has not yet been established. This paper reports the synthesis of oligomers composed of alternating 6-amino-6-deoxyaldonic acid and 6-aminohexanoic acid units, and their cyclisations to 14-, 28- and 42-membered rings.

Keywords: cyclic peptide; cyclodextrin; sugar amino acid; macrocyclic lactam; biopolymer.
* Corresponding author. Tel.: +44-1865-277386; fax: +44-1865-277378; e-mail: george.fleet@chem.ox.ac.uk

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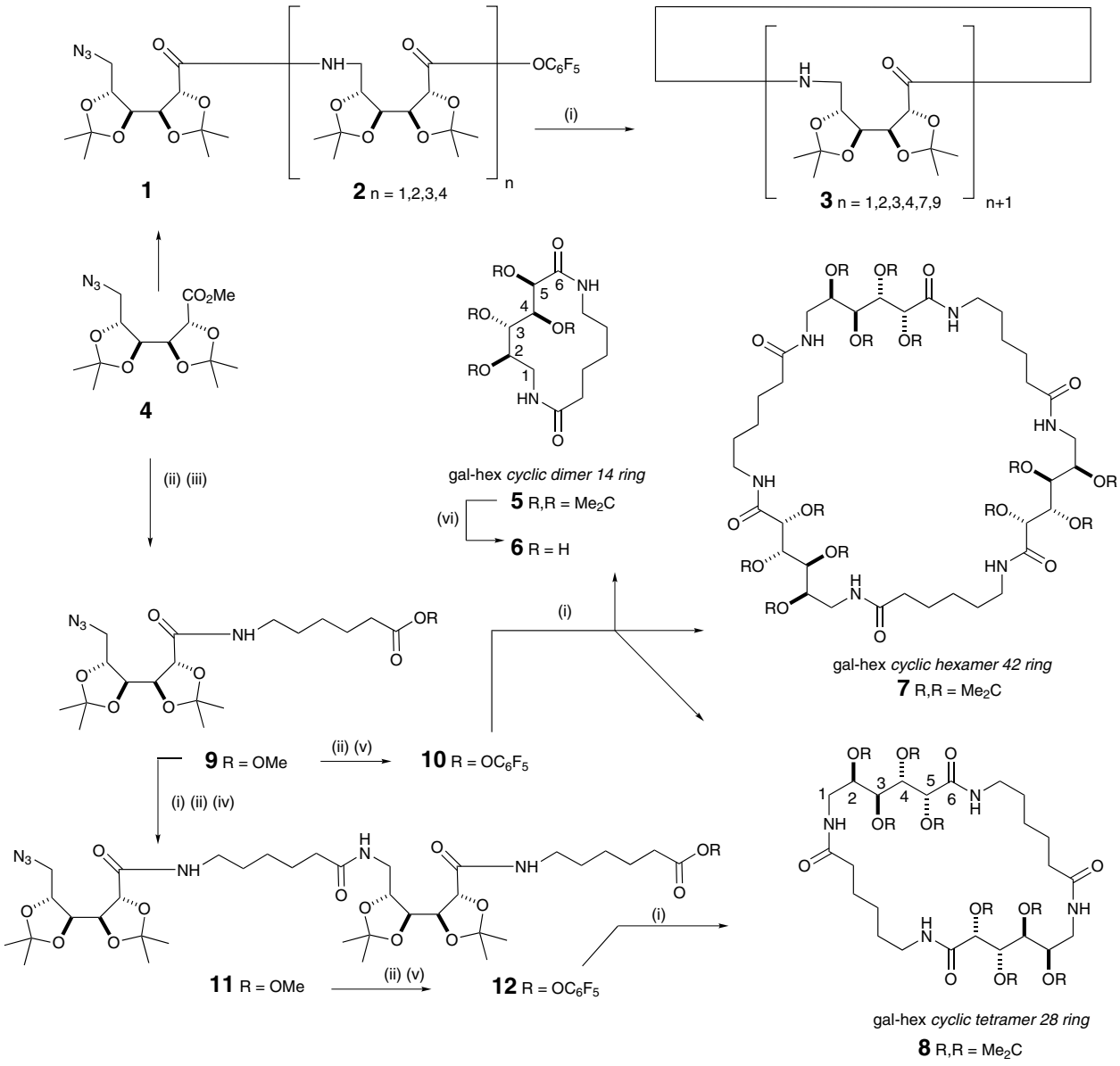
2. Synthesis and cyclisations of mixed [*gal-hex*] oligomers

The azidoester **4**[2] was converted into the linear *gal-hex* dimer **10** and tetramer **12** PFP esters of 6-amino-6-deoxy-D-galactonic acid [*gal*] and 6-aminohexanoic acid [*hex*] by standard peptide coupling methodology (Scheme 1).

Thus the methyl ester **4** was treated with sodium hydroxide in aqueous dioxane to give the corresponding acid, which with methyl 6-aminohexanoate hydrochloride in the presence of diisopropylethylamine (DIPEA) and *O*-(1*H*-benzotriazol-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) gave the linear *gal-hex* dimer **9** in 91% yield. Hydrogenation of the azido ester **9** in methanol in the presence of palladium black gave the corresponding amino ester, which was coupled with the acid formed by hydrolysis of **9**, with subsequent activation with DIPEA and TBTU to give the linear *gal-hex* tetramer **11** in 68% yield. Further reactions of **9** and **11** with sodium hydroxide in aqueous dioxane, followed by activation of the resulting carboxylic acid in dioxane by EDCI and treatment with pentafluorophenol afforded the *gal-hex* linear dimeric **10** and tetrameric **12** PFP esters in 86% and 75% yields, respectively.

Hydrogenation of the linear *gal-hex* dimer PFP ester **10** in the presence of palladium black in dioxane at a concentration of 18 mg/mL gave a separable[3] mixture of the cyclic dimer **5**, tetramer **8** and hexamer **7** in a ratio of



Scheme 1. Reagents and conditions: (i) H_2, Pd black, dioxane, room temperature and pressure; (ii) NaOH, H_2O, dioxane, then Amberlite IR-120 H^+; (iii) $H_2N(CH_2)_5COOH{\cdot}HCl$, DIPEA, TBTU; (iv) DIPEA, TBTU; (v) C_6F_5OH, EDCI; (vi) Amberlyst-15, H_2O, dioxane.

1:2:1 and a combined yield of 91%. It is possible that the tetramer **8** (or the hexamer **7**) might have been a catenane structure; however hydrogenation of the tetramer PFP ester **12** gave the *same* cyclic *gal-hex* tetramer **8** showing that this is a monocyclic structure. Removal of the acetonides in **5** by treatment with Amberlyst-15 acidic resin gave the deprotected *gal-hex* cyclic dimer **6**,[4] the structure of which was firmly established[5] by X-ray crystallographic analysis (Fig. 1).

3. Synthesis and cyclisations of mixed [*man-hex*] oligomers

The azido-*mannono*-lactone **13**[6] was treated with methyl 6-aminohexanoate hydrochloride in the presence of DIPEA to afford the partially protected linear *man-hex* dimer **14** in 96% yield. (Scheme 2). Subsequent treatment with dimethoxypropane in the presence of *p*-toluenesulfonic acid (*p*-TSA) gave the fully protected dimer **19** in 90% yield.

Hydrogenation of the protected methyl ester **19** in methanol in the presence of palladium black gave the corresponding amino ester, which was coupled with the acid formed by hydrolysis of **19**, with subsequent activation with DIPEA and TBTU to give the linear *man-hex* tetramer **23** in 90% yield. Hydrolysis of the *man-hex* methyl esters **14**, **19** and **23** by sodium hydroxide in aqueous dioxane, followed by activation of the resulting carboxylic acids in dioxane by EDCI and treatment with pentafluorophenol gave the corresponding *man-hex* linear PFP esters **15**, **20** and **24** in 64%, 98% and 90% yields, respectively.

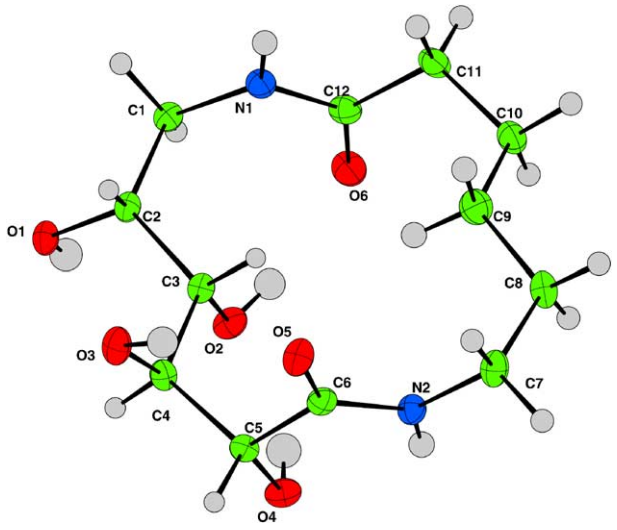
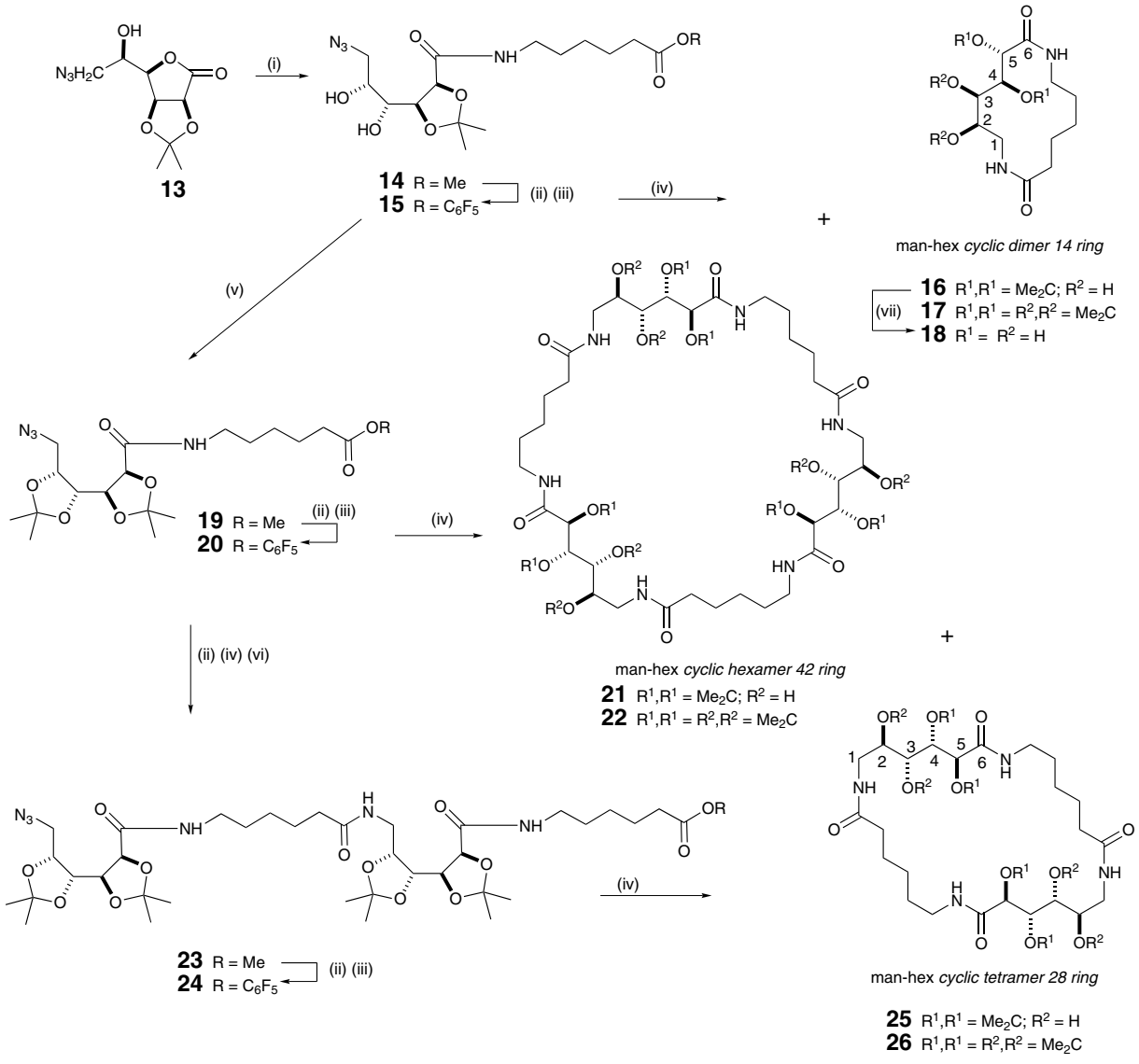


Figure 1. X-ray crystal structure of deprotected *gal-hex* dimer **6** with crystallographic numbering.

Reduction of the each of the PFP esters by hydrogenation caused cyclooligomerisation to macrocycles. Thus hydrogenation of the dimer **15** in dioxane at a concentration of 16 mg/mL gave a separable mixture of the partially protected 14-membered **16** (21% yield), 28-membered **25** (37% yield) and 42-membered **21** (15% yield) ring *man-hex* cyclic oligomers (73% combined yield of cyclic materials). Treatment of **16** with acid ion exchange resin in aqueous dioxane gave the fully deprotected macrocyclic lactam **18**[7] in quantitative yield.

Hydrogenation of the fully protected *man-hex* dimer **20** in dioxane at a concentration of 10 mg/mL gave **17**:**26**:**22** in a ratio of approximately 1:3:1 and a combined yield of 86%; these cyclic oligomers were more difficult to separate by flash chromatography. Hydrogenation of the linear *man-hex* tetrameric PFP ester **24** in dioxane at a concentration of 1 mg/mL gave the same *man-hex* 28-membered ring **26** in an isolated yield of 79%.



Scheme 2. Reagents and conditions: (i) $H_2N(CH_2)_5COOH{\cdot}HCl$, DIPEA; (ii) NaOH, H_2O, dioxane, then Amberlite IR-120 H^+; (iii) C_6F_5OH, EDCI; (iv) H_2, Pd black, dioxane; (v) $Me_2C(OMe)_2$, *p*-TSA; (vi) DIPEA, TBTU; (vii) Amberlyst-15, H_2O, dioxane.

4. Summary

This paper shows that a series of 14-, 28- and 42-membered macrocyclic lactams may be formed in good yields from linear oligomers derived from ε-amino acids. The preceding paper provided a specific example of a fully hydroxylated system, which also underwent efficient cyclisation; this work suggests that the construction of a family of macrocycles with the structural characteristics of both cyclodextrins and cyclic peptides will be relatively easy and thus provide access to a novel new class of biomaterials.[8]

References and Notes

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2. Long, D. D.; Stetz, R. J. E.; Nash, R. J.; Marquess, D. G.; Lloyd, J. D.; Winters, A. L.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 901–908.
3. Elution of products by gradient elution from 100% ethyl acetate to 93%:7%, then 91%:9% ethyl acetate/methanol.
4. Selected data for deprotected *gal-hex* cyclic dimer **6**: $[\alpha]_D^{24}$ −22.0 (*c* 0.65, D_2O); mp > 220 °C; ν_{max} (thin film, Ge plate): 3326 cm^{-1} (br s, O–H, N–H), 1643 cm^{-1} (C═O, amides I), 1550 cm^{-1} (C═O, amides II); ^1H NMR δ_H (400 MHz, D_2O): 1.14 (2H, m, *J* 7.6, H-9, H-9′), 1.39–1.49 (2H, m, H-8, H-8′), 1.56 (2H, a-quin, *J* 7.2, H-10, H-10′), 2.14–2.77 (2H, m, *J* 6.3, H-11, H-11′), 3.16 (1H, dd, $J_{1,1'}$ 13.3, $J_{1,2}$ 4.8, H-1), 3.21–3.32 (2H, m, H-7, H-7′), 3.41–3.48 (2H, m, H-1′, H-3), 3.89 (1H, dd, $J_{4,3}$ 8.0, $J_{4,5}$ 5.1, H-4), 3.95 (1H, a-dd, *J* 11.3, $J_{2,1}$ 4.8, H-2), 4.24 (1H, d, $J_{5,4}$ 5.1, H-5); ^{13}C NMR δ_C (100 MHz, D_2O): 25.01 (C-9), 25.19 (C-10), 28.43 (C-8), 35.32 (C-11), 38.91 (C-7), 39.83 (C-1), 67.98 (C-2), 69.77 (C-3), 71.24 (C-4), 74.29 (C-5), 173.83, 177.64 (2×*C*ONH). MS *m*/*z* (ES-): 288.80 ([M−H]$^-$, 100%); HRMS: $C_{12}H_{21}N_2O_6$ ([M−H]$^-$) calcd 289.1400, found 289.1393.
5. Crystallographic data have been deposited with the CCDC, reference no. CCDC 220310. Crystal size 0.16×0.18×0.40 mm. Crystal system: orthorhombic, space group *P* 2_1 2_1 2_1. Unit-cell parameters: a =7.7898(2), b = 11.0897(2), c = 15.6046(4) Å, volume = 1348.03(5) $Å^3$. Calculated density: 1.430 mg/m^3. X-ray data were measured using a Nonius KappaCCD diffractometer using graphite-monochromated Mo-Kα radiation, λ = 0.71073 Å. Data were collected using ω scans, $2\theta \leqslant 55°$. 10735 reflections measured, of which 1790 unique, R_{int} = 0.028, 1586 reflections with $I > 3\sigma(I)$ used in refinement. Absorption corrections were applied using the multi-scan technique (transmission range 0.96, 0.98, μ = 0.115). The structure was solved by direct methods (SIR92). Full-matrix least-squares refinement on F was carried out using the CRYSTALS program suite. 205 parameters included were included in the refinement: Coordinates and anisotropic thermal parameters of non-hydrogen atoms; coordinates and isotropic thermal parameters of OH and NH hydrogen atoms. Other hydrogen atoms were positioned geometrically. After convergence, R = 0.0272, wR = 0.0313, residual electron density (min, max) = −0.17, 0.14 e$Å^{-3}$.
6. Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F. *Tetrahedron* **2002**, *58*, 6907–6911.
7. Selected data for deprotected *man-hex* cyclic dimer **18**: $[\alpha]_D^{25}$: −30.1 (*c* 0.95, H_2O); mp > 220 °C, needles contract and amalgamate into amorphous solid above 217 °C; ν_{max} (thin film, Ge plate): 3307 cm^{-1} (br s, O–H, N–H), 1638 cm^{-1} (C═O, amides I); ^1H NMR δ_H (500 MHz, D_2O): 1.13–1.23 (2H, m, H-9, H-9′), 1.40–1.48 (1H, m, H-8), 1.53–1.66 (3H, m, H-8′, H-10, H-10′), 2.30 (2H, t, *J* 6.2, H-11, H-11′), 2.97 (1H, a-ddd, $J_{7,7'}$ 13.5, *J* 6.1, *J* 3.5, H-7), 3.08 (1H, dd, $J_{1,1'}$ 14.6, *J* 3.0, H-1), 3.43 (1H, a-d, $J_{3,2}$ 9.6, H-3), 3.63 (1H, a-ddd, $J_{7',7}$ 13.5, *J* 9.7, *J* 3.3, H-7′), 3.75 (1H, a-dt, $J_{2,3}$ 9.6, *J* 2.3, H-2), 3.97 (1H, dd, $J_{1',1}$ 14.6, *J* 1.6, H-1′), 4.24 (1H, a-d, $J_{4,5}$ 3.2, H-4), 4.41 (1H, d, $J_{5,4}$ 3.2, H-5); ^{13}C NMR δ_C (125 MHz, D_2O): 25.23 (C-9), 25.42 (C-10), 28.69 (C-8), 35.61 (C-11), 38.86 (C-7), 41.30 (C-1), 67.55 (C-4), 68.49 (C-2), 70.52 (C-3), 77.27 (C-5), 174.19, 178.29 (2×*C*ONH). MS *m*/*z* (ES-): 289.14 ([M–H]$^-$, 100%); HRMS: $C_{12}H_{21}N_2O_6$ ([M−H]$^-$) calcd 289.1400, found 289.1407.

8. A BBSRC CASE award with Smith & Nephew [to B.A.M.] is gratefully acknowledged.