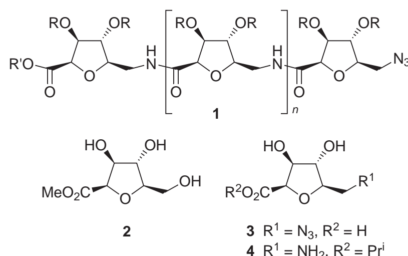
Synthesis of oligomers of tetrahydrofuran amino acids: furanose carbopeptoids

Martin D. Smith,[a] Daniel D. Long,[a] Daniel G. Marquess,[b,c] Timothy D. W. Claridge and George W. J. Fleet*[a]†

[a] *Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY*
[b] *Glaxo Wellcome Ltd., Gunnels Wood Road, Stevenage, Herts, UK SG1 2NY*
[c] *Advanced Medicine Inc., 270 Littlefield Avenue, Suite B, South San Francisco, CA 94080, USA*

An acid catalysed ring rearrangement of a triflate derivative of D-mannono-γ-lactone 6 is the key step in the synthesis of the *C*-glycosyl sugar amino acid derivatives 3 and 4, examples of carbohydrate amino acid building blocks with specific conformational preferences suitable for incorporation into combinatorial amide libraries; homo-oligomerisation *via* solution phase coupling procedures affords furanose carbopeptoids 1 which adopt novel solution state secondary structures.

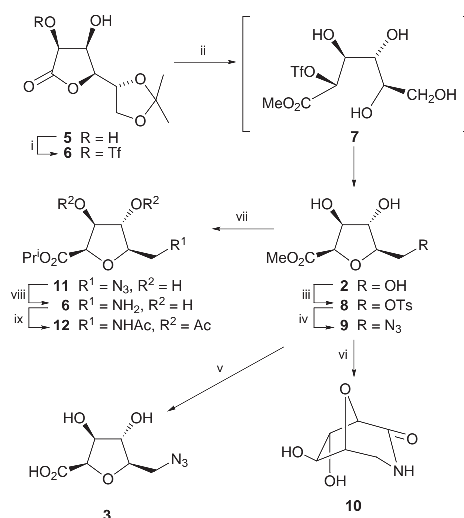
Carbohydrate amino acids are attractive building blocks for the routine incorporation of carbohydrate moieties into combinatorial libraries by standard peptide coupling techniques.[1] The conformational influence of the sugar backbone on peptide chains has been exploited in the rational design of non-peptide peptidomimetics.[2] Homo-oligomeric sugar amino acids ('carbopeptoids'[3]) based upon a pyranose template have been prepared by solution[4] and solid[5] phase approaches, though to date there are no furanose[6] analogues. Here we describe the synthesis of a *C*-glycofuranosyl sugar amino acid analogue and its oligomerisation to materials which adopt a well-defined secondary structure.



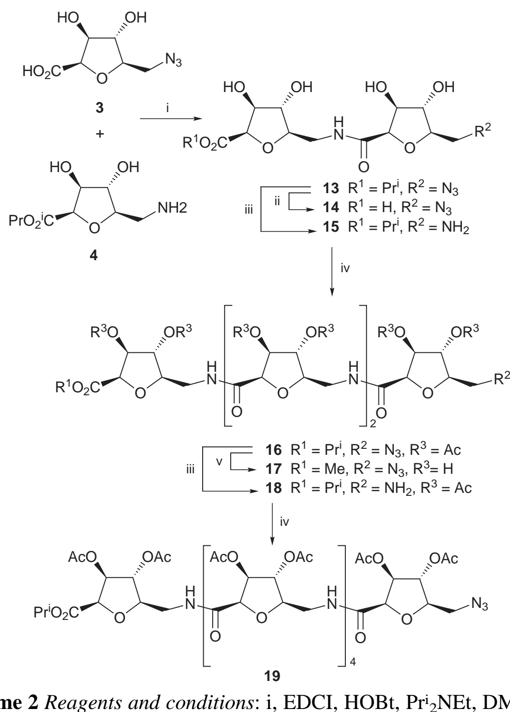
2-*O*-Triflates (trifluoromethanesulfonates) of γ- and δ-lactones in basic[7] or acidic[8] MeOH give good to excellent yields of highly substituted tetrahydrofurancarboxylates. Such a procedure has recently been utilised for the synthesis of *C*-glycosides of glucofuranose,[9] which have provided scaffolds for the generation of glucofuranose libraries. For the synthesis of the *C*-arabinosyl derivative **2**, the triflate **6** is required; in order to effect esterification at C-2, it is necessary to protect the primary hydroxy group at C-6 in D-mannonolactone as its kinetic monoacetonide **5**, easily accessible in 74% yield from the diacetonide of D-mannose.[10] Treatment of the diol **5** with Tf_2O in CH_2Cl_2 in the presence of pyridine caused highly regioselective esterification of the hydroxy group at C-2 to give the stable triflate **6**, which may be isolated in 85% yield; **6** has previously been described but in a significantly poorer yield.[11] Treatment of the crude triflate **6** with HCl in MeOH gave the required ester **2** in 84% yield from **5**, providing multigram quantities of **2** in an overall yield of 62% from D-mannose. The key transformation of **6** to **2** by treatment with acidic MeOH involves hydrolysis of the side chain acetonide, methanolysis of the lactone, followed by intramolecular S_N2-like closure of the resulting open chain hydroxy triflate **7** with inversion of configuration at C-2 (Scheme 1). Although it is possible that intermediates such as **7** could undergo alternative closure to a tetrahydropyran, resulting from attack by the C-6 rather than the C-5 hydroxy group, no *C*-glycopyranosides were isolated; ring closures to *C*-glycopyranoses by nucleophilic displacement at C-2 of a sugar are rare.[12]

The strategy adopted for the synthesis of carbopeptoids **1** utilises well-established peptide bond forming methodology. For the synthesis of sugar amino acid building blocks **3** and **4**, it is necessary to introduce nitrogen at C-6. Selective esterification of **2** with toluene-*p*-sulfonyl chloride in pyridine (to give the 6-*O*-tosyl derivative **8**) and subsequent displacement of the sulfonate ester with NaN_3 in DMF at 90 °C gave the azide **9** in 72% yield over two steps.[13] Hydrolysis of the methyl ester with aq. NaOH and purification by ion exchange chromatography afforded the carboxylic acid **3** in quantitative yield. Catalytic hydrogenation of the methyl ester **9** gave the bicyclic lactam **10** *via* a non-isolable amine; a more hindered ester is required to enable isolation of the required 6-amino component **4**. Accordingly, transesterification of the methyl ester **9** with K_2CO_3 in Pr^iOH gave the isopropyl derivative **11** in 79% yield.[14] Hydrogenation of the azide **11** in the presence of Pd-C in Pr^iOH afforded the amine **4** as the major product together with an unidentified and inseparable minor component; the highly polar amine **4**, characterised as its triacetate **12**, (90% yield from **11**),was used without purification in all further reactions.

Coupling of **4** and **3** was then performed using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in DMF in the presence of 1-hydroxybenzotriazole (HOBt). This reaction allowed the isolation of the dimeric compound **13** in 74% yield (from the azide **11**) as an easily handled solid (Scheme 2). No protection of the secondary hydroxy groups is necessary during the coupling procedure. Iteration of the coupling procedure gave ready access to the tetramer **1** ($n = 2$) and the hexamer **1** ($n = 4$). The dimer **13** was treated with aq. NaOH and purified by ion exchange chromatography to afford



Scheme 1 *Reagents and conditions*: i, Tf_2O, Py, CH_2Cl_2; ii, 1% HCl in MeOH; iii, TsCl, Py; iv, NaN_3, DMF; v, 0.5 M aq. NaOH, dioxane, ion exchange; vi, H_2, Pd, EtOH; vii, K_2CO_3, Pr^iOH; viii, H_2, Pd, Pr^iOH; ix, Ac_2O, Py



Scheme 2 *Reagents and conditions*: i, EDCI, HOBt, $Pr^i{}_2NEt$, DMF; ii, 0.5 M aq. NaOH, dioxane, then Amberlite IR-120 (H^+); iii, H_2, Pd, Pr^iOH; iv, **14** (1 equiv.), EDCI, HOBt, $Pr^i{}_2NEt$, DMF, then Ac_2O, Py; v, NaOMe, MeOH, then Amberlite IR-120 (H^+)

the free acid **14** in quantitative yield. Additionally the *N*-terminal azide in **13** was reduced with H_2 in the presence of Pd-C to afford the amine **15**. Coupling of the dimeric building blocks **14** and **15** was performed using EDCI in DMF in the presence of HOBt. The reaction mixture was treated with Ac_2O in pyridine to facilitate isolation of the tetramer **16**[15] (55% from **13**) from which the acetate groups can be removed with NaOMe in MeOH to afford the deprotected carbopeptoid **17** in quantitative yield. Hydrogenation of the tetramer **16** in the presence of Pd gave the *N*-terminal amine **18** which was coupled crude to the dimeric acid **14** using EDCI in DMF in the presence of HOBt. Treatment of the reaction mixture with Ac_2O in pyridine gave the hexamer **19** in 68% yield from the tetramer **16**.

The ease with which highly functionalised tetrahydrofurans, such as **4**, can be synthesised is likely to offer opportunities for the production of a range of carbohydrate amino acid building blocks with specific conformational preferences suitable for incorporation into combinatorial amide libraries. The diversity of possible structures afforded by a carbohydrate template in terms of backbone stereochemistries and protecting group manipulations allows formation of hydrophobic or hydrophilic—and thus water soluble—derivatives. Efficient unprotected oligomerisation to give compounds with well-defined secondary structure emphasizes the versatility of the sugar amino acid building block and alludes to the possibility of a more rational design tailored to specific applications. The following paper provides evidence for conformational preferences of the hexamer **19** and the tetramer **16**; NMR and molecular dynamics indicate that both adopt a well-defined secondary structure based around a repeating β-turn mimic stabilised by intramolecular hydrogen bonds.[16]

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Notes and References

† E-mail: george.fleet@chem.ox.ac.uk

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13 *Selected data* for **2**: δ_H(500 MHz, CD_3CN) 3.58 (1H, d, *J* 3.7, OH-4), 3.64–3.74 (3H, m, H-6, H-6′, OH-6), 3.70 (3H, s, CO_2*Me*), 3.88 (1H, q, *J* 3.2, H-5), 4.03–4.05 (1H, m, H-4), 4.12 (1H, ddd, *J* 4.3, 1.9, 8.4, H-3), 4.33 (1H, d, *J* 8.4, OH-3), 4.59 (1H, d, *J* 4.3, H-2).
14 *Selected data* for **11**: δ_H(500 MHz, CD_3OD) 1.27 (6H, t, *J* 6.2, Me_2CH), 3.38 (1H, dd, *J* 4.7, 12.7, H-6′), 3.62, (1H, dd, *J* 7.5, 12.7, H-6′), 3.91–3.94 (1H, m, H-5), 3.95 (1H, dd, *J* 2.8, 5.7, H-4), 4.26 (1H, dd, *J* 2.8, 5.1, H-3), 4.61 (1H, d, *J* 5.1, H-2), 5.07 (1H, septet, *J* 6.2, Me_2C*H*).
15 *Selected data* for **16** (500 MHz, $CDCl_3$, 298 K):

	Ring **A**	Ring **B**	Ring **C**	Ring **D**
$\delta_C(C^1)$	167.81	168.11	167.68	167.15
$\delta_H(C^2)$	4.669	4.692	4.708	4.687
$\delta_C(C^2)$	81.02	81.74	81.38	78.93
$\delta_H(C^3)$	5.646	5.559	5.495	5.475
$\delta_C(C^3)$	76.08	75.57	76.01	76.66
$\delta_H(C^4)$	4.904	4.837	5.003	5.250
$\delta_C(C^4)$	78.40	78.06	77.68	77.57
$\delta_H(C^5)$	4.153	4.027	4.123	4.055
$\delta_C(C^5)$	85.00	85.18	85.00	83.19
$\delta_H(C^6)$	3.708/ 3.461	4.027/ 3.224	3.861/ 3.228	3.781/ 3.481
$\delta_C(C^6)$	51.43	41.28	41.28	40.48
δ_H(NH)	—	6.910	8.025	8.191

Carbopeptoids are identified alphabetically from the N- to the C-terminus; protons on each ring are numbered according to IUPAC recommendations on carbohydrate nomenclature.

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