Novel Oligosaccharide Mimetics by Solid-phase Synthesis†

Claus Müller, Eric Kitas and Hans Peter Wessel*

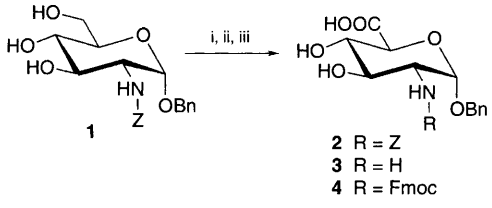
F. Hoffmann-La Roche Ltd, Pharma Division, Preclinical Research, CH-4002 Basel, Switzerland

The amide-linked tetrasaccharide mimetic **8** is synthesised on a solid phase support from a carbohydrate amino acid building block without hydroxy protection using activation with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU)

Mimetics of oligosaccharides are obtained by modification of the glycosidic bond. The formal replacement of the interglycosidic oxygen by a methylene group leads to C-disaccharides[1] which have been synthesised by a variety of approaches.[2] Pyranoses coupled directly or *via* substituted methylenes or also more extended units are close analogues. Using this concept, mainly disaccharide and a few trisaccharide[3] mimetics have been prepared.

Alternatively, an amide function may serve to link carbohydrate moieties.[4] Thus, carbohydrate amino acids can be employed to build up oligomers using methodologies well established in peptide chemistry. While an earlier publication by Yoshimura *et al.*[5] on amide-linked disaccharides has so far received little attention, we have recently synthesised (in solution) an amide-linked tetrasaccharide mimetic using normuramic acid derivatives as building blocks.[6] Here we describe the homologation of a carbohydrate amino acid using a solid-phase method.

For the construction of carbohydrate amino acid oligomers we chose a glucosaminuronic acid derivative as a building block. Since amide-linked disaccharide analogues have already been shown to display low solubility,[5] the application of solid-phase technology was particularly attractive for this example. For the conversion of benzyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside **1**[7,8] TEMPO oxidation[9] was employed to give the known[7,10] uronic acid **2**. Although the cleavage of a benzyloxycarbonyl (Z) protecting group usually occurs with good selectivity in the presence of a benzyl α-D-pyranoside, the hydrogenation of **2** furnished only moderate yields of **3** due to some deblocking of the anomeric centre. For the peptide synthesis the fluoren-9-ylmethoxycarbonyl (Fmoc)[11,12] protection scheme was applied using building block **4** (Scheme 1).‡



Scheme 1 *Reagents and conditions*: i, NaOCl, TEMPO, KBr, Bu_4NCl, H_2O, CH_2Cl_2, 0 °C, 1.5 h, 67%; ii, H_2, Pd/C, MeOH, dioxane, room temp., 8 h, 45% (recovered starting material 37%); iii, Me_3SiCl, diisopropylethylamine (DIPEA), CH_2Cl_2, reflux, 18 h; FmocCl, 3 h, 75%

The solid-phase synthesis§ was performed on a benzhydrylamine polystyrene resin **5**, functionalised with an Fmoc-amide linker, *p*-[(*R,S*)-α-1-(9*H*-fluoren-9-yl)methoxyformamido-2,4-dimethoxybenzyl]phenoxyacetic acid, based on the Rink-resin[13] (Scheme 2). While the attachment of the carbohydrate amino acid **4** to this solid support using *in situ* activation with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TATU)[14] was, under a variety of reaction conditions, not complete in a single step, the coupling was repeated to give quantitative formation of **6** according to the Kaiser test.[15] Subsequent amide-bond forming required only single couplings. Tetramer **8**¶ was released from the resin under acidic reaction conditions. The crude product was pure by ^1H NMR. However, reversed phase (C18) HPLC purification indicated the presence of small amounts of tetramethyluronium N-capped derivatives of the dimer and of the trimer which were identified by mass spectrometry.‖ No trace of *O*-acylated side products was found.

This methodology should pave the way to libraries[16] of oligosaccharide mimetics composed of carbohydrate amino acids alone, or including other natural or unnatural amino acids.

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Footnotes

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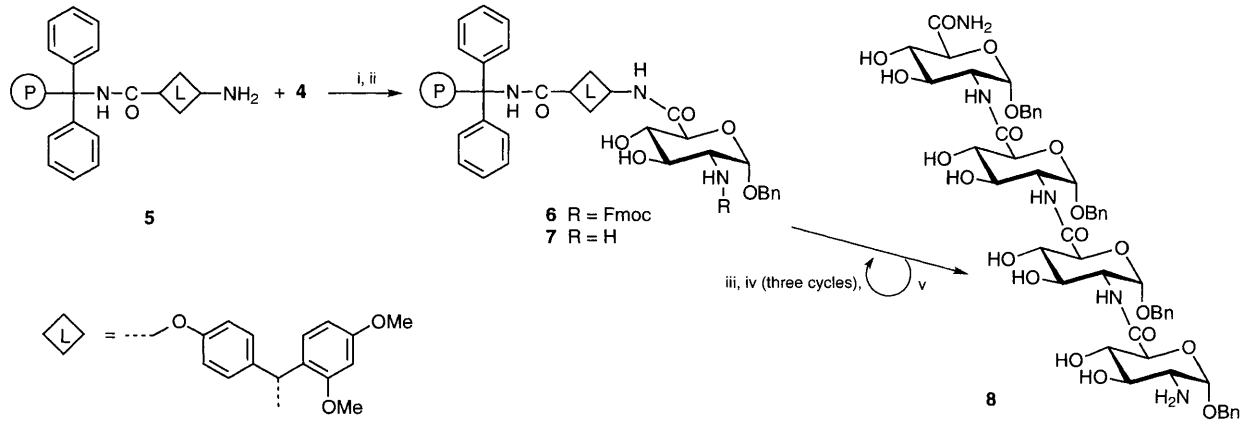
‡ Analytical data were in agreement with the structures assigned; selected analytical data for **4**: $[\alpha]_D^{20}$ +74.6 (*c* 0.5, DMF); MS (ionspray) *m/z* 504.5 [100%, (M − H)$^-$].



Scheme 2 *Reagents and conditions*: i, Fmoc-amide linker-benzhydrylamine polystyrene (0.16 mmol g^{-1}), **4** (1.75 equiv.), TATU (1.75 equiv.), DIPEA (4.4 equiv.), DMF, room temp., 60 + 20 min; ii, 20% piperidine in DMF, room temp., 2 × 7 min; iii, **4** (2.0 equiv.), TATU (2.0 equiv.), DIPEA (5.0 equiv.), room temp., 45 min per cycle; iv, 20% piperidine in DMF, room temp., 2 × 7 min; v, 50% TFA, CH_2Cl_2, room temp., 2 × 2 h, 70% (based on quantity and functional group density of resin)

§ Solid-phase synthesis was performed on a Peptide Synthesizer SP650 (Labortec AG).

¶ Selected analytical data for **8**: $[\alpha]_D^{20}$ +149.5 (*c* 0.4, Me_2SO); MS (ionspray) *m/z* 1100.4 [100%, $(M + Na)^+$]. The signals of the pyranose rings in the ^1H NMR spectrum of **8** were completely assigned.

‖ Analogous side products were obtained with HBTU in solid phase peptide synthesis.[17]

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