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Solution and solid phase synthesis of hetarylene-carbopeptoids. A new type of peptidomimetics

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Abstract—Ready access to a new class of peptidomimetics has been demonstrated by the synthesis of hetarylene-carbopeptoids using a hydroxyalkylfuran-aminoacid **7** as a novel scaffold.

Peptides and proteins are logical targets for mimicry[1] due to their fundamental role in biological processes and because of the pharmacological limitations of natural bioactive peptides.[2] Potentially useful peptidomimetics should resist in vivo hydrolysis and present some conformational bias.[3] With these goals in mind, Gellman et al.[4] have prepared peptides from rigidified cyclic β-aminoacids. Nicolaou et al.[5] first introduced the use of sugars as a means to increase the rigidity of peptidomimetics, and introduced the name of 'carbopeptoid' for such oligomers that are peptide-bond linked carbohydrates. Some of them have interesting biological properties, including HIV replication inhibition.[6] Aminoglycoside antibiotic mimetics, made from *N*-acetylneuraminic acid, have been reported.[7] On their hand, Fleet et al.[8] have reported peptidomimetics adopting interesting secondary structures because of the carbohydrate-derived tetrahydrofuran systems they contain.

Searching for new molecules that can be assembled with themselves and/or other aminoacids using well established combinatorial techniques, we propose a new scaffold Aij (Fig. 1) which contains a polyol fragment (i) whose length and chirality are given by the aldose used to make it, and a 5-alkylfuran moiety, the alkyl group (j) of which can be varied on changing the acyl acetate employed in the condensation with the starting

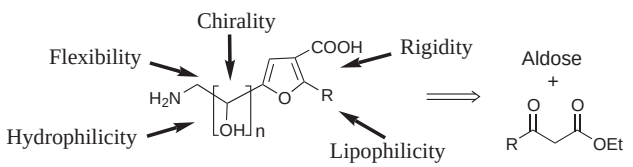
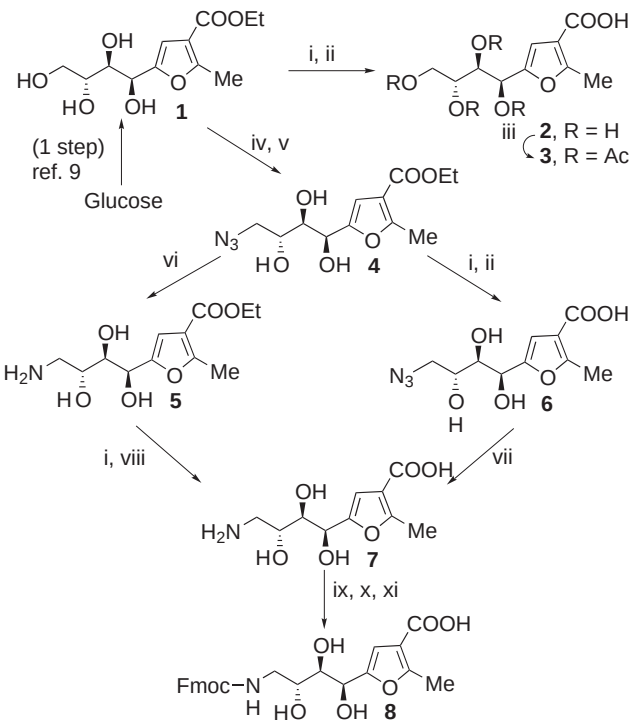


Figure 1. Scaffold Aij.



Scheme 1. Building blocks. *Reagents and conditions*: (i) NaOH 1 M, EtOH, 60°C, 3 h; (ii) IR-120 (H^+), MeOH (80% for **2**, 90% for **6**, two steps); (iii) Ac_2O, Py (quant.); (iv) TsCl, Py, −15°C, 2 h (57%); (v) NaN_3, DMF, 110°C, 2.5 h (70%); (vi) H_2, Pd/C, EtOH, 15 min (98%); (vii) H_2, Pd/C, MeOH, 2 h (60%); (viii), 1 M HCl (80% for two steps); (ix) TMSCl, Py, 1 h; (x) FmocCl, 1 h; (xi) H_2O, 2 h (95% for three steps).

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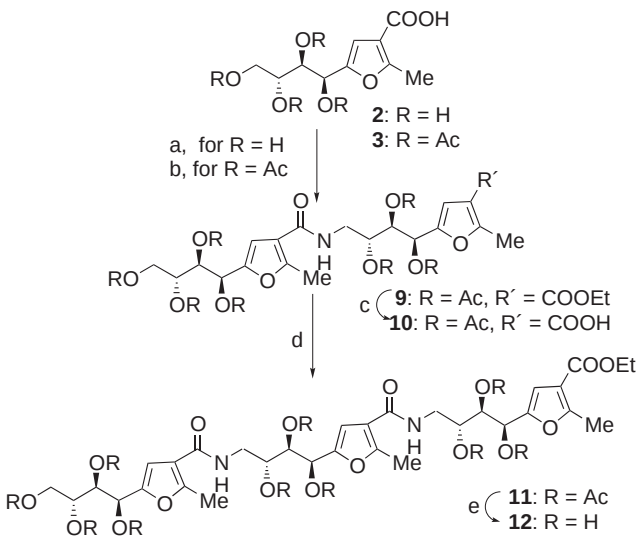
aldose.[9] We now describe the synthesis of one member of the sub-library Aij (i, $n=3$, configuration: D-arabino) and demonstrate that it can be combined to generate oligomers by applying either solution or solid phase processes.

The polyhydroxy and alkylfuran moieties make these compounds attractive, as complex biochemical processes involve molecular recognition based on polar (e.g. hydrogen bonds) and hydrophobic interactions.[10]

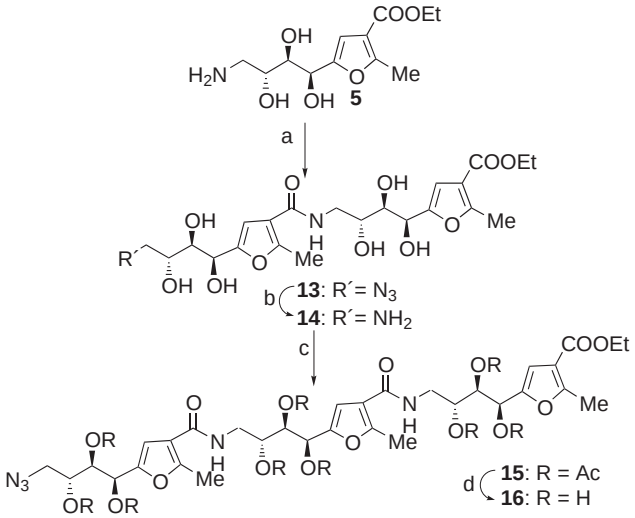
The synthesis of the building blocks (Scheme 1) starts from **1**.[9] Regioselective tosylation, followed by S_N2 displacement with NaN_3 gave the azidoester **4**. Subsequent hydrogenation furnished **5**. Hydrolysis of esters **1** and **4** provided carboxylic acids **2** and **6**, respectively. Reduction of the azide **6** delivered aminoacid **7** which was *N*-protected as the Fmoc derivative **8**. This required protection of the polyol as a polysilyl ether in order to avoid formation of carbonates (a regioselective direct reaction gives complex mixtures and a low yield for **8**). Koole's procedure[11] (TMSCl/py, then FmocCl/py, then H_2O) led to **8** in 95% overall yield.

The strategy of head elongation (Scheme 2) is based on the condensation of acid **2** with the aminoester **5** under Mukaiyama conditions.[12] This gave, after acetylation, the dimeric derivative **9**. The latter was easily hydrolyzed into **10** and coupled again with the aminoester **5** to give the trimer **11**.[13] When using a mixture of DCM/DMF, the protected per-acetate **3** and **5**, the yield was increased.

For the tail elongation (Scheme 3), the coupling of unprotected **5** and **6** was carried out in DMF with



Scheme 2. Head elongation. *Reagents and conditions*: (a) (i) 2 equiv. Ph_3P, 2 equiv. of PyS-SPy, DMF, 2 equiv. of **5**, 12 h, (ii) Ac_2O, Py, 12 h (54% for two steps); (b) (i) 2 equiv. of Ph_3P, 2 equiv. PyS-SPy, DCM:DMF (3:1), 1 equiv. of **5**, 6 h, (ii) Ac_2O, Py, 12 h (74% for two steps); (c) (i) 1 M NaOH, EtOH, 10 h, 60°C, (ii) IR-120 (H^+), MeOH, (iii) Ac_2O, Py (89% for three steps); (d) b (60% for two steps); (e) NaOMe, MeOH (quant.).

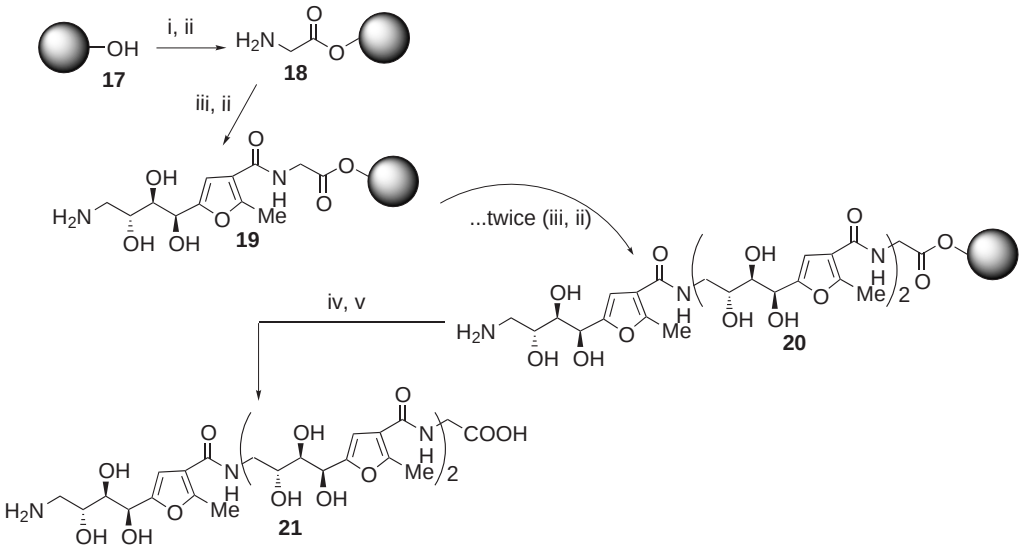


Scheme 3. Tail elongation. *Reagents and conditions*: (a) PyBOP, DIPEA, DMF, 1 equiv. of **6**, 45 min (62%); (b) H_2, Pd/C, EtOH, 30 min (95%); (c) (i) a, (ii) Ac_2O, Py, 12 h (60% for two steps); (d) NaOMe, MeOH (quant.).

PyBOP (benzotriazolyloxy-trispyrrolidino phosphonium hexafluorophosphate) and DIPEA[14] (*N*,*N*-diisopropylethylamine) as activating reagents. After 45 min the dimer **13** was isolated in 70% yield. Reduction of the azide and a subsequent coupling reaction gave the corresponding trimer that was purified in the per-acetylated form **15**[15] in 60% yield.

In order to demonstrate the viability of the use of solid phase techniques for incorporating our scaffold Aij into oligomers, we envisaged the synthesis of the pseudotetrapeptide **21** on a solid support (Scheme 4). We have used the Fmoc strategy and the HMBA-AM resin in which the linker is the 4-hydroxymethyl benzoic acid.[16] The couplings were accomplished without protection of the OH groups of the amino acid **8**. The commercially available Fmoc-glycine was attached to the OH resin using 2,6-dichlorobenzoyl chloride and pyridine.[17] This offers a double advantage: it favours the anchoring to the HO resin by avoiding competitive reactions with the free OH groups of **8**, and facilitates the final cleavage of the oligomer from the resin. Subsequent treatment with piperidine gave the solid-supported amine **18**. The Fmoc-aminoacid **8** was then coupled by treatment with PyBOP and DIPEA in DMF, affording the immobilized dimer **19**. The process was repeated twice to obtain the polymer-bound compound **20** that was removed from the solid support with 1 M NaOH and THF as co-solvent to assist swelling of the resin. The aminoacid **21**[18] presents high water solubility. This method could provide a library of oligomers with high bioavailability.

In conclusion, we have synthesized a new class of compounds that represent new leads for combinatorial chemistry in glycopeptidomimetic design. The ease of preparation, their structural diversity with respect to



Scheme 4. Solid phase synthesis: Fmoc strategy. *Reagents and conditions*: (i) 2,6-dichlorobenzoyl chloride, py, DMF, Fmoc-Gly-OH; (ii) 20% PIP/DMF; (iii) PyBOP, DIPEA, DMF, 1 equiv. of **8**; (iv) 1 M, NaOH, THF; (v) 1 M AcOH (60% overall).

functionality and stereochemistry and their stability may lead to new bioactive compounds.

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18. Selected data for **21**: δ_C (125.7 MHz, D_2O) 178.0, 168.0, 167.4, 157.9, 157.8, 152.9 (3C), 116.8 (3C), 108.0, 107.8 (3C), 75.2, 70.8, 70.7, 68.7, 67.8, 67.6, 44.4, 43.2, 42.8 (2C), 14.1, 14.0 (3C).