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Orthogonally protected carbohydrate-based scaffolds

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Abstract—A series of orthogonally protected polyaminated carbohydrate scaffolds have been prepared on a multi-gram scale.

1. Introduction

Although biologically relevant peptidomimetics are regularly reported with activities on a wide range of receptors and enzymes, most of them are constructed around an achiral template and the use of chiral scaffolds has little precedence. Good activity of any drug is related to the precise positioning of crucial pharmacophoric groups within the biological target binding site leading to optimal shape and interacting group orientation. One of the main tasks is therefore to identify a correct scaffold. Towards this end, monosaccharide units are attractive synthons, since a judicious choice of the carbohydrate core would properly position the various appendages that are anchored on the hydroxyl groups into the binding site.[1] In fact, carbohydrate-based scaffolds for peptidomimetics were first introduced by Hirschmann et al. a decade ago and led to potent somatostatin mimics.[2]

The stereodiversity potential of carbohydrate-based templates (made possible by the availability of a wide range of monosaccharides) was the impetus for initiating the preparation of carbohydrate-based scaffolds for peptidomimetics. Based on this concept, we developed xylose-based RGDF mimics exhibiting encouraging activity towards integrins (Fig. 1, **1**).[3]

At this point, we decided to expand the scope of this approach and designed orthogonally protected scaffolds based on carbohydrate templates. The design of this type of scaffold was dictated by the desire to disclose versatile chiral templates for peptidomimetics. Two main issues have to be addressed: (1) the orthogonal protection of each anchor; and (2) the projected large scale preparation of such compounds which requires practical and high yielding steps.

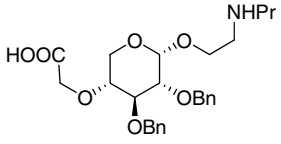

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Figure 1. Carbohydrate-based peptidomimetics, integrin antagonists.

Polyamino sugars have also recently shown to be building blocks in the preparation of oligosaccharide mimics.[4] This report prompted us to disclose our efforts in the preparation of orthogonally protected polyamino sugar scaffolds.

2. First-generation orthogonally protected glucosediamine

A first scaffold **8** based on the glucose core was designed. Its synthesis, outlined in Scheme 1, began with the protection of the free hydroxyl of the readily available methyl 2-(acetylamino)-2-deoxy-4,6-*O*-benzylidene α-D-glucopyranoside **2**[5] by a bulky pivaloyl group to furnish **3**. Execution of the synthetic plan with the corresponding acetyl analogue led to an undesired migration at a later stage in the synthesis. Regioselective opening of the benzylidene acetal ring was next achieved by treatment with an equimolar mixture of triethylsilane and trifluoroacetic acid to provide compound **4**.[6] This method

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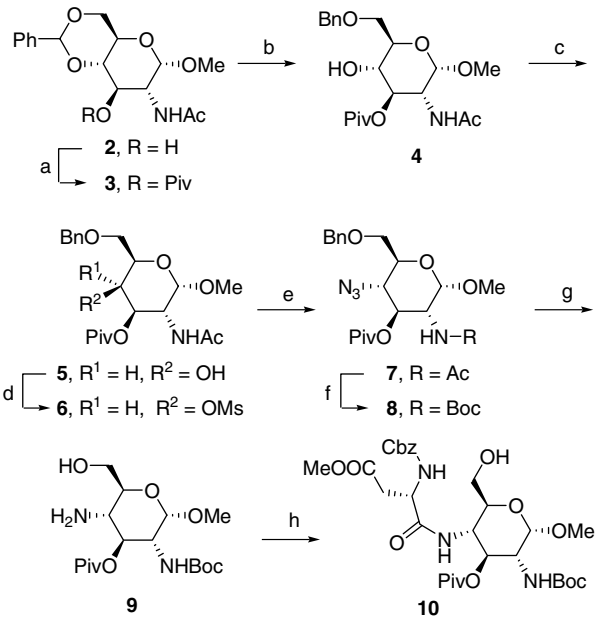


Scheme 1. Preparation and use of the orthogonally protected scaffold **8**. Reagents and conditions: (a) PivCl, Et_3N, 0 °C then rt, CH_2Cl_2, 87%; (b) Et_3SiH, TFA, CH_2Cl_2, 0 °C then rt, 90%; (c) (i) Tf_2O, pyridine, 0 °C then rt, CH_2Cl_2; (ii) $NaNO_2$, DMF, 76% (over 2 steps); (d) MsCl, Et_3N, 0 °C then rt, CH_2Cl_2; (e) NaN_3, DMF, 110 °C, 88% (over 2 steps); (f) (i) Boc_2O, DMAP, THF, reflux; (ii) $NH_2NH_2{\cdot}xH_2O$, MeOH/THF, 85% (over 2 steps); (g) H_2, 10% Pd–C, dioxane, 79%; (h) Cbz-Asp(OMe)-OH, HBTU, HOBt, DIPEA, 85%.

was more conveniently scaled up than the usual combination of $NaBH_3CN$ and ethereal HCl.[7]

The crucial double inversion was next investigated and began by triflation of the remaining free hydroxyl of **4**.[8] The resulting triflate proved to be fairly unstable on silica gel, and was therefore used without further purification. Thus, hydrolysis of the crude triflate proceeded smoothly, affording the galactosamine intermediate **5** in good yield and in diastereomerically pure form. Subsequent mesylation produced **6**, which was reactive towards sodium azide used as a masked amine group. Again, the reaction took place with complete inversion yielding **7**. Alternative preparation of the chloro counterpart using PPh_3–CCl_4 and displacement with sodium azide gave **7** in a modest yield owing to the observed competitive elimination.

Access to the Boc protected amine **8** was made possible by a formal exchange between acetyl and Boc group that proceeded smoothly using previously reported mild conditions.[9] Thus, upon treatment with Boc_2O and DMAP, **7** was converted into the diprotected amine, which was isolated and then reacted with hydrazine hydrate to afford the fully protected advanced intermediate **8**. To evaluate the use of **9** as an orthogonally protected scaffold, reduction of the azide and simultaneous deprotection of the benzyl ether group was accomplished under catalytic hydrogenolysis conditions to give **9**. The corresponding amine was next coupled with an amino acid leading to pseudopeptide **10**. The choice of aspartic acid was dictated by the additional functional groups featured by this amino acid. The free hydroxyl group was well tolerated under these conditions, although a negligible amount of side products was observed.

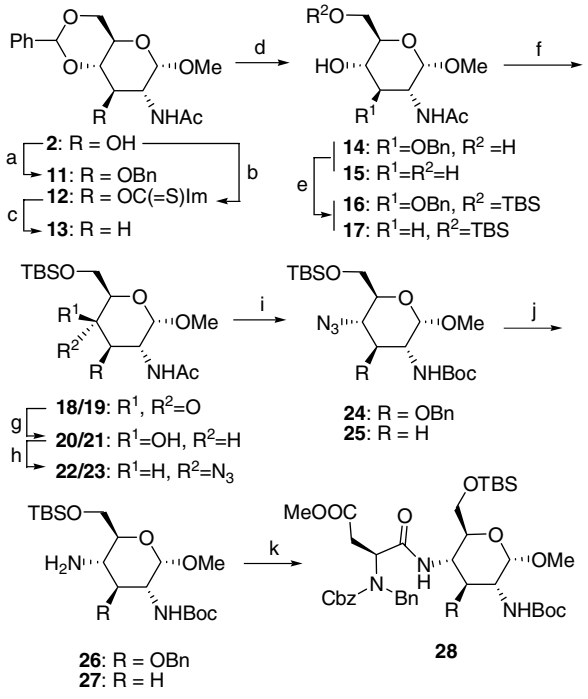
The depicted route to **8** allowed for the preparation of multi-gram quantities from commercially available derivative **2**. The chemoselective removal of the protecting groups led us to revise the selection of orthogonal protecting groups.

3. Second-generation orthogonally protected polyaminated carbohydrates

3.1. *Gluco* diamine

A new set of protecting groups was envisaged. A silyl ether was introduced at position 6 and a benzyl ether at position 3. Polyfunctionalized carbohydrates such as **8** or **24** would be bulky and removal of a hydroxyl group would simplify the structure. Thus, aiming at mimicking peptides, we also prepared the corresponding deoxy derivative **25**.

The synthesis shown in Scheme 2 started with the benzylation or stepwise Barton and McCombie[10] deoxygenation of readily available glucosamide **2** leading to **11**

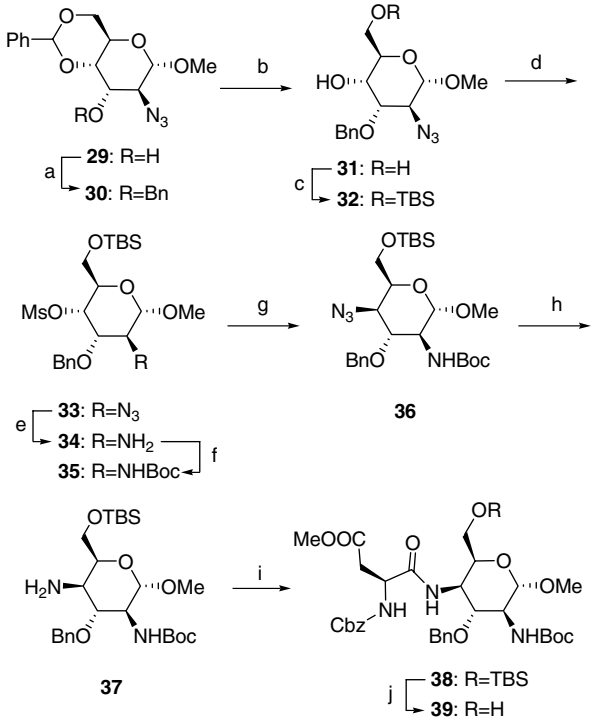


Scheme 2. Preparation and use of the orthogonally protected scaffolds **24** and **25**. Reagents and conditions: (a) NaH, BnBr, DMF, 91%; (b) $(Im)_2CS$, DMAP, THF, reflux, 92%; (c) Bu_3SnH, toluene, reflux, 91%; (d) AcOH/THF/H_2O, 40 °C, 92% (**14**), 88% (**15**); (e) TBSCl, pyridine, 67% (**16**), TBSCl, DMF, Im, 96% (**17**); (f) TPAP, NMO, CH_2Cl_2, 4 Å MS, 98% (**18**), 97% (**19**); (g) L-selectride, THF, −78 °C, 80% (**20**), 83% (**21**); (h) DPPA, DEAD, PPh_3, CH_2Cl_2, 62% (**22**), 89% (**23**); (i) Boc_2O, DMAP, THF, reflux; then $NH_2NH_2{\cdot}xH_2O$, MeOH, 92% (**24**), 92% (**25**); (j) H_2, 10% Pd–C, dioxane, 83% (**26**), 83% (**27**); (k) Cbz(Bn)-Asp(OMe)-OH, HBTU, HOBt, DIPEA, DMF, 54%.

and **13**, respectively. The benzylidene acetals were next hydrolyzed upon acidic treatment, giving the diols **14** and **15** which were regioselectively protected as the corresponding silyl ethers **16** and **17**. Investigation of the inversion and azide introduction steps led to the optimized oxidation/stereoselective reduction sequence shown in Scheme 2 followed by a Bose–Mitsunobu reaction[11] which completed the sequence. The use of such scaffolds was evaluated by hydrogenation followed by coupling with an amino acid to afford structures **28** in acceptable yields.

3.2. *Ido* diamine

With these first scaffolds and optimized syntheses in hand, we explored the preparation of another stereoisomer. The idose scaffold was selected and prepared as shown in Scheme 3. Although the presented scaffolds are polydeoxy, polyamino allosides, the stereochemistry of the scaffolds is that of idosides. We therefore, will use 'idose' throughout this manuscript. Readily available compound **29**[12] was used as starting material. The sequence used to prepare compound **24** was adapted for the preparation of its ido counterpart **36**. Opening of the cyclic acetal was followed by silylation and introduction of a masked amine on position 4 with complete inversion. This sequence led to the orthogonally protected scaffold **36** in good yields. As for the previous scaffolds, reduction and coupling were found to be high yielding. The chemoselective reduction of the azide in presence of the benzyl ether was achieved using the Staudinger reduction.[13]



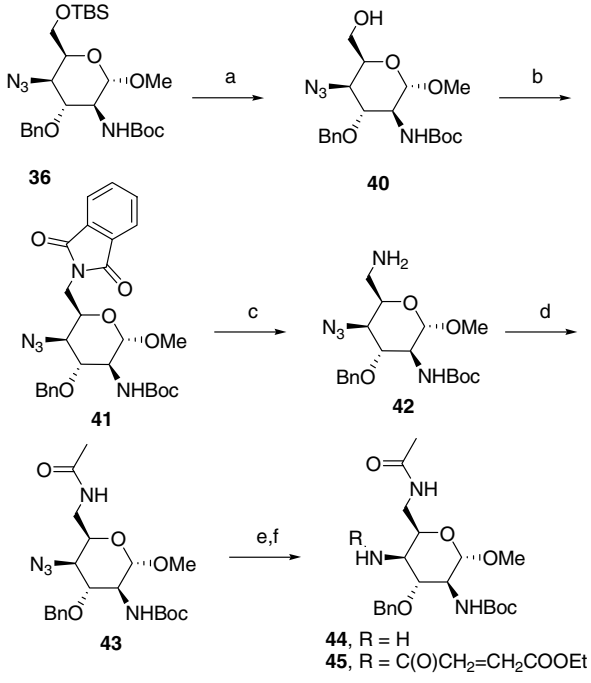
Scheme 3. Preparation and use of the orthogonally protected scaffold **36**. Reagents and conditions: (a) NaH, BnBr, DMF, 89%; (b) AcOH/H_2O, 100 °C, quant.; (c) TBSCl, Im, DMF, 85%; (d) MsCl, Et_3N, CH_2Cl_2, 84%; (e) PPh_3, THF then H_2O, 60 °C, 79% or H_2, 5% Pd–C, EtOH, 81%; (f) Boc_2O, Et_3N, CH_2Cl_2, 93%; (g) NaN_3, DMF, 100 °C, 80%; (h) H_2, 5% Pd–C, EtOH, 88%; (i) Cbz-Asp(OMe)-OH, HBTU, DIPEA, DMF, 82%; (j) AcOH/H_2O/THF, 95%.

3.3. *Ido* triamine

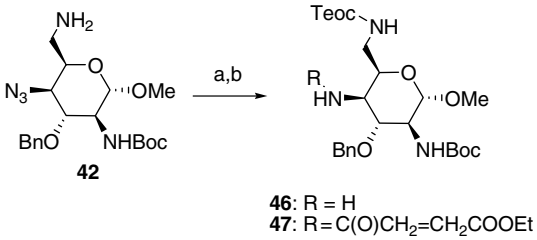
We next explored the design and synthesis of triamine derivatives. For this purpose, derivative **36** was deprotected and reacted under Mitsunobu conditions[14] to afford the orthogonally protected triamine **41**. Attempts were made to orthogonally functionalize positions 4 or 6. For instance, position 6 was quantitatively unmasked by treatment with hydrazine leading to the primary amine **42** which was quantitatively acetylated. The second amine was next deprotected under Staudinger conditions[13] then coupled with an acid leading to the highly functionalized scaffold **45**. The overall sequence shown in Scheme 4 was achieved in reasonable yields.

In parallel, we have shown that position 4 can be reacted first through reduction of the azide followed by regioselective reprotection of position 6 (Scheme 5).

The thus obtained 4-amino derivative can be subsequently coupled leading to the orthogonally protected scaffold **47**. This last scaffold features a Teoc group sensitive to TBAF treatment, an ester that can be saponified, a double bond that can be further functionalized or reduced, a benzyl ether that can be cleaved by hydrogenolysis, and a Boc carbamate that can be removed under acidic conditions. These various functional groups can be treated in this order in the preparation of



Scheme 4. Preparation and use of the orthogonally protected scaffold **41**. Reagents and conditions: (a) 1 M TBAF/THF, 89%; (b) phthalimide, PPh_3, DEAD, THF, 79%; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, quant.; (d) Ac_2O, K_2CO_3, CH_2Cl_2, quant.; (e) PPh_3, THF then H_2O, 60 °C, 73%; (f) RCOOH, HOBt, EDC, DIPEA, DMF, 67%.



Scheme 5. Reagents and conditions: (a) (i) PPh_3, THF/H_2O, DMF, 68%; (ii) $TMSCH_2CH_2OH$, phosgene, toluene, Et_3N, 32% (along with di-Teoc, 16%); (b) EtOOCCH=CHCOOH, HOBT, EDC, DIPEA, DMF, 75%.

highly functionalized peptidomimetics. Similarly, the scaffold **41** can be selectively deprotected with hydrazine (position 6), triphenylphosphine (position 4), hydrogen (position 3) and trifluoroacetic acid (position 2).

In summary, we have designed and prepared original carbohydrate-based scaffolds featuring differentially/orthogonally protected groups as potential anchors. Their synthesis called for key inversion steps. The syntheses were carried out on a multi-gram scale. The scaffolds **8**, **24**, **25**, **30**, **41** and **47** are the first members of a larger series well suited for preparation of stereodiverse libraries. Further applications to the preparation of biologically relevant compounds are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.081.

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