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# Alkylated Sugar Amino Acids: A New Entry toward Highly Functionalized Dipeptide Isosters

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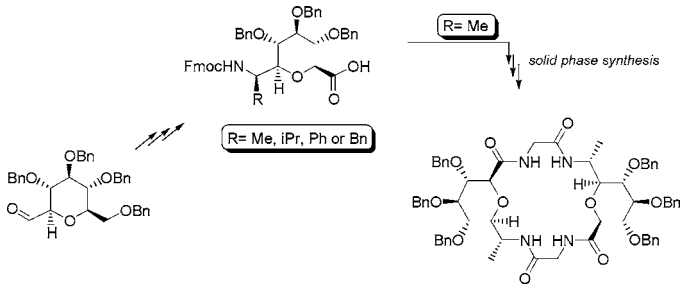
## ABSTRACT




**Novel highly functionalized dipeptide isosters are synthesized via a diastereoselective alkyl/arylation protocol of a glucose-derived (R)-*tert*-butanesulfinylimine. One of these novel sugar amino acid derivatives, a D-Ala-Ser/Thr isostere, was applied in a peptide synthesis protocol to afford a cyclic tetramer.**

An important aim in bioorganic chemistry entails the design and synthesis of oligopeptide mimetics that are locked in the biological relevant conformation of their natural counterparts. The diversity in structure and stereochemistry inherent to monosaccharides, combined with well-established synthetic procedures for their derivatization, has resulted in the preparation of a broad range of carbohydrate-based peptidomimetics.[1] Sugar amino acids (SAAs),[2] carbohydrate-derived compounds having an amine and a carboxylate appended to a furan/pyran core, are of particular interest not only as scaffolds[3] for the introduction of specific functionalities to the parent sugar core but also as conformationally constrained dipeptide isosters. In this context, Kessler and co-workers analyzed the conformational properties of a series of SAA residues incorporated in enkephalin and somatostatin oligopeptides.[2j,4] It was found that glucose derived δ-SAA **1**, a conformationally restricted dipeptide isostere, induces

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a $\beta$-turn conformation when incorporated in selected oligopeptide sequences. A closer inspection of SAA **1** reveals structural similarity to a Gly-Ser/Thr dipeptide,[5] with the functionalized tetrahydropyran core stemming from the original carbohydrate resembling, in part, the serine/threonine side chains. Several examples of SAAs, in which the furan/pyran core is modified to contain functionalities resembling amino acid side chains other than Ser/Thr, have been reported in recent years.[2]

However, the reported dipeptide isosters, as exemplified by **1**, normally contain a primary amine functionality that is employed for incorporation in oligopeptide sequences. In other words, the reported SAA-based dipeptide isosters almost without exception display glycine-like properties. Any synthetic sequence enabling the construction of SAAs that are alkylated at the $\delta$-position, as in **2** (Figure 1), will result

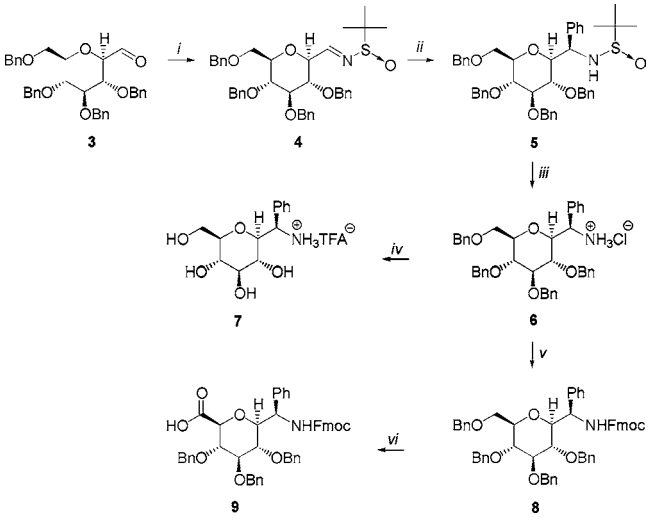

**Figure 1.** Structures of known $\delta$-SAA **1**, a Gly-Ser/Thr mimic, and the here reported alkylated $\delta$-SAA **2**.

in the preparation of dipeptide isosters other than those including glycine. With this aim in mind, we set out to develop a suitable route to the synthesis of $\delta$-substituted SAAs, the initial results of which are presented here.[6]

The key step in our synthetic strategy entails the introduction of alkyl/aryl functionality via diastereoselective addition on a carbohydrate-derived sulfinimine. The applicability of the new SAA derivatives in a standard peptide synthesis protocol is demonstrated by the use of one of these, the conformationally restricted protected D-Ala-Ser/Thr mimic SAA **11**, for the construction of cyclic tetramer **19**.

Our synthetic strategy is exemplified by the synthesis of SAA **9**. Condensation of the known formyl tetra-*O*-benzyl-$\beta$-D-*C*-glucopyranoside **3**[7] with commercially available (*R*)-*tert*-butanesulfinyl amide (Ellman's reagent)[8] in the presence of anhydrous $CuSO_4$ in DCM[9] (70%, Scheme 1) provided

**Scheme 1.** Synthesis of Sugar Amino Acids **7** and **9**[a]




[a] Reagents and conditions: (i) (*R*)-*tert*-butylsulfinamide, anhydrous $CuSO_4$, DCM, rt, 24 h, 70%. (ii) PhMgBr, $PhCH_3$, −78 °C, 3 h. (iii) HCl/MeOH, rt, 30 min. (iv) (a) $Boc_2O$, DiPEA, DCM, rt, 4 h, 73%; (b) $H_2$, Pd/C, MeOH, acetone, rt, 12 h, 86%; (c) 95% TFA/$H_2O$, rt, 2 h, quantitative. (v) Fmoc-OSu, DiPEA, DCM, 1,4-dioxane, rt, 1 h. (vi) (a) $ZnCl_2$, AcOH, $Ac_2O$, rt, 12 h; (b) HCl/MeOH, rt, 6 h; (c) TEMPO, BAIB, DCM/$H_2O$, rt, 12 h.

carbohydrate-derived sulfinimine **4**. Treatment of **4** with PhMgCl led to the formation of sulfinamide **5** in high diastereoisomeric excess (>95%, de), as judged by NMR analysis of the crude product.

To determine the stereochemical outcome of the alkylation reaction, compound **5** was desulfinylated under the influence of HCl in MeOH to give HCl salt **6**, which was subsequently transformed to the corresponding *t*-butoxycarbonylate ($Boc_2O$, DiPEA, DCM). Ensuing Pd/C hydrogenolysis of the benzyl ethers followed by acid-mediated removal of the Boc protective group (95% TFA in $H_2O$) afforded known TFA-salt **7**.[10] All analytical and spectroscopic data of **7** were consistent with those reported in the literature. The *Re*-site addition of the Grignard reagent to sulfinimine **3** suggests the involvement in chelation of an oxygen of the sugar moiety with the magnesium reagent, besides chelation of the oxygen of the sulfinyl functionality.[11]

In continuation of the synthesis of SAA **9**, HCl salt **6** was protected as the Fmoc derivative (Fmoc-OSu, DiPEA, DCM/

(3) Smith, A. B., III; Sasho, S.; Barwis, B. A.; Sprengeler, P.; Barbosa, J.; Hirschmann, R.; Cooperman, B. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3133−3136.

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(7) (a) For synthesis of formyl tetra-*O*-benzyl-$\beta$-D-*C*-glucopyranoside see: Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737−740. (b) Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404−6412. (c) Sánchez, M. E.; Michelet, V.; Besnier, I.; Genêt, J. P. *Synlett* **1994**, 705−708. (d) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13−16.

(8) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913−9914.

(9) Use of a stronger Lewis acid such as Ti(O-$^i$Pr)$_4$ resulted in a lower yield (50%).

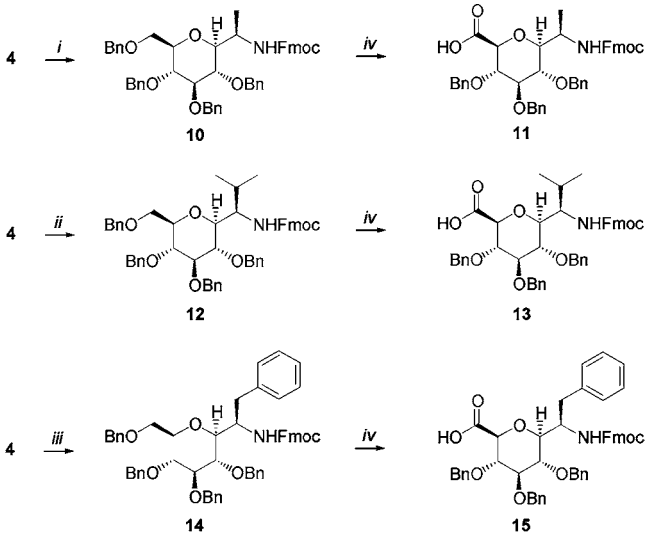
(10) Schmidt, R. R.; Dietrich, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1328−1329.

(11) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39−46.

dioxane) to give compound **8** as a single diastereoisomer in 63% yield (two steps, based on **5**). Selective debenzylation of the primary hydroxyl functionality in **8** was achieved by treatment with anhydrous $ZnCl_2$ in AcOH and $Ac_2O$, followed by acidic deacetylation (HCl in MeOH) and oxidation using TEMPO and BAIB (bisiodobenzene diacetate) as co-oxidants,[12] providing suitably protected target SAA **9** in a yield of 80% based on three steps starting from **6**.

As the next research objective, the construction of substituted SAAs **11**, **13**, and **15** was explored. Treatment of sulfinimine **4** with MeMgBr or *i*-PrMgCl under the conditions described above, followed by removal of the sulfoxyl auxiliary and Fmoc protection, afforded the fully protected methyl- and *i*-propyl-substituted amines **10** (71%) and **12** (61%), respectively, as single diastereoisomers (Scheme 2). Interestingly, treatment of **4** with benzylmagnesium bromide in $PhCH_3$ led to the formation of **14** in only 18% yield. To our satisfaction, compound **14** could be prepared in improved yield (50%) by changing the solvent system from dichloromethane to toluene and by adding an equimolar amount of $BF_3{\cdot}OEt_2$ to the reaction mixture.[13]

**Scheme 2.** Synthesis of Sugar Amino Acids **11**, **13**, and **15**[a]

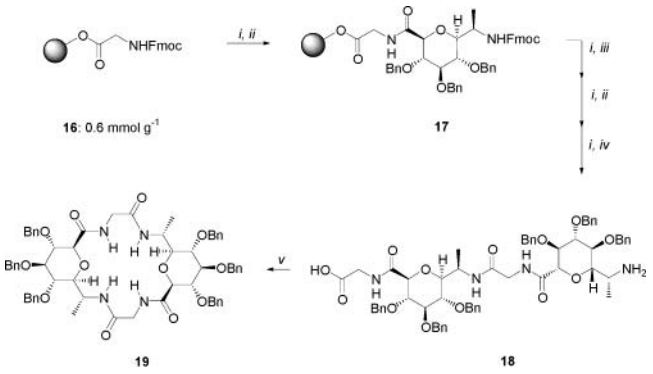



[a] Reagents and conditions: (*i*) (a) MeMgBr, $PhCH_3$, −78 °C; (b) HCl/MeOH, rt, 30 min; (c) Fmoc-OSu, DiPEA, DCM, 1,4-dioxane, rt, 1 h (71% over three steps). (ii) (a) *i*-PrMgCl, −78 °C, $PhCH_3$; (b) HCl/MeOH, rt, 30 min; (c) Fmoc-OSu, DiPEA, DCM, 1,4-dioxane, rt, 1 h (61% over three steps). (iii) (a) BnMgCl, DCM, $BF_3{\cdot}OEt_2$ (2 equiv), −78 °C; (b) HCl/MeOH, rt, 30 min; (c) Fmoc-OSu, DiPEA, DCM, 1,4-dioxane, rt, 1 h (50% over three steps). (iv) (a) $ZnCl_2$, AcOH, $Ac_2O$, rt, 12 h; (b) HCl/MeOH, rt, 6 h; (c) TEMPO, BAIB, DCM/$H_2O$, rt, 12 h (**11**, 64% over three steps; **13**, 74% over three steps; **15**, 64% over three steps).

pounds **10**, **12**, and **14** were converted into the corresponding carboxylic acid group, furnishing protected SAAs **11**, **13**, and **15**, respectively, in each case in good overall yield.

At this point we set out to investigate whether the obtained novel alkylated $\delta$-SAAs, having a secondary amine functionality, can be readily incorporated in oligomeric sequences using standard peptide synthesis protocols. For this purpose, protected D-Ala-Ser/Thr isoster **11** was condensed with glycine-functionalized Wang resin **16** (HATU, HOAt, 2,4,6-collidine, Scheme 3). The thus obtained immobilized product

**Scheme 3.** Solid-Phase Synthesis of Cyclic Oligomer **19** with Sugar Amino Acid **11**[a]




[a] Reagents and conditions: (i) 20% piperidine in DMF, rt (2 × 20 min). (ii) (a) **11** (1 equiv), HATU (0.9 equiv), HOAt (0.9 equiv), 2,4,6-collidine (20 equiv), DMF, DCM, rt, 2 h (double coupling); (b) capping: $Ac_2O$ (5 vol %) and DiPEA (6 vol %) in DMF (10 min). (iii) Fmoc-Gly-OH (5 equiv), HATU (4.95 equiv), HOAt (4.95 equiv), 2,4,6-collidine (20 equiv), DMF, DCM, rt, 2 h (double coupling); (b) capping. (iv) TFA/DCM (1/1, v/v), rt, 30 min. (v) HATU (2 equiv), HOAt (2 equiv), 2,4,6-collidine (20 equiv), DMF, 4 °C, 24 h.

**17** was readily transformed into linear tetramer **18** by removal of the Fmoc protecting group, repetition of the coupling/deprotection steps, and TFA-mediated cleavage from the solid support. Cyclization of the linear oligomer (HATU, HOAt, 2,4,6-collidine) under high dilution conditions ($c$ = 0.001 M) afforded, after purification by silica gel column chromatography, benzylated cyclic tetramer **19** in an excellent 74% overall yield.

In conclusion, we have presented a versatile synthesis toward novel SAA dipeptide isosters. Variation in the nature of the nucleophile employed in the key alkylation step and potential further elaborations (for instance, addition of allylmagnesium bromide, followed by oxidation/cleavage of the double bond) should give access to SAA-based dipeptide isosters having the equivalent of heteroatom-containing

(12) (a) DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977. (b) Epp, J. B.; Widlandski, T. S. *J. Org. Chem.* **1999**, *64*, 293−295.

(13) Reaction of **4** with BnMgCl as the organometallic reagent in $PhCH_3$ gave compound **14** in only 18% yield. The formation of side-products (via base-induced elimination), could be suppressed by performing the reaction in DCM in the presence of 2 equiv of $BF_3{\cdot}OEt_2$, without affecting the stereochemical outcome of the reaction. A likewise addition of 2 equiv of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ in the addition of PhMgBr and **4** did not affect the stereochemical outcome or yield. See: Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396−3397.

amino acid side chains. Furthermore, variation of the nature of the chiral sulfinimine or the carbohydrate template should provide control over the stereoselectivity of the addition step, giving access to the equivalent side chain of L-amino acids. Finally, the presence of the added substituent will have a profound effect on the conformational behavior of this type of dipeptide isosters, and oligopeptides containing them. It should be noted that peptides featuring **1** still possess partial conformational flexibility due to rotational freedom around the N−C−C−O dihedral angle.[4] Current research activities are focused on both exploring the synthetic scope of our strategy and the conformational analysis of linear and cyclic oligopeptides containing SAAs with the general structure **2**.

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**Supporting Information Available:** Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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