Synthesis of alkylated sugar amino acids: conformationally restricted L-Xaa-L-Ser/Thr mimics†

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Two synthetic strategies for the generation of δ-substituted pyranoid sugar amino acids (SAAs) are evaluated. The first employs chiral nonracemic *tert*-butane sulfinamides as key reagents. Regardless of the stereochemistry of the applied sulfinamide, the product formed has a stereochemistry resembling that of a D amino acid at C7. Direct Grignard reaction on formyl-tetra-*O*-benzyl-β-D-*C*-glucopyranoside in the second strategy and subsequent Mitsunobu inversion, yields the L,L-dipeptide isosters.

Introduction

As part of our ongoing research on artificial peptide-like materials, we recently reported the synthesis of glucopyranose-based sugar amino acids (SAAs) **1** (Fig. 1).[1] In dipeptide isosteres **1**, the stereocentre at C2 has the *S*-configuration, thereby resembling the α-carbon in L-serine or L-threonine.[2] The secondary amine at the N-terminus (C7) in **1** resembles the side-chain at the α-carbon of amino acids other than glycine. By tuning the nature of the R^1 group, functionalities corresponding to specific amino acid side-chains can be incorporated into the SAAs.[3] This feature distinguishes compounds **1** from SAAs reported in the literature,[4] of which the large majority are primary amines.[5] As a whole, SAAs **1** can be viewed as conformationally constrained H-Xaa-Ser/Thr-OH mimics. The configuration of C7 corresponds to that of the α-carbons in D-amino acids, rather than the proteinogenic L-amino acids. In contrast to stereochemical control over the C-terminal portion, which originates from selection of the carbohydrate template, controlling the configuration of the newly introduced stereocentre at C7 stems from asymmetric organic synthesis. The work presented here concerns adaptation of the synthetic strategy we applied to prepare SAAs **1** to provide C7-*S* configured SAA building blocks **2**.

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Protected SAAs **1** were previously prepared using the stereoselective alkylation of *R*-*tert*-butanesulfinimide **4**, which was obtained by the condensation of formyl tetra-*O*-benzyl-β-D-*C*-glucopyranoside **3**[6] with *R*-*tert*-butanesulfinyl amide[7] (Scheme 1). Alkylation of compound **4**, subsequent acid-mediated hydrolysis of the *R*-*tert*-butanesulfonyl group and instalment of the Fmoc protective group gave compound **7**, which could be transformed into carboxylate **8** by selective acidolysis of the primary benzyl ether, ester hydrolysis and oxidation. The alkylation of sulfinimide **4** proceeds in good diastereoselectivity. For instance, reaction of **4** with 3 equivalents of MeMgBr in methylene chloride at −78 °C gave *R*-methyl adduct **5** in 20-fold excess over the other diastereoisomer **6**. Similar results were obtained by using toluene as a solvent. Performing the alkylation in THF resulted in a drop in diastereoselectivity (**5**–**6** = 13 : 1).

Either the *R*-*tert*-butanesulfinyl chiral auxiliary or the chiral carbohydrate template, or a combination of both may be responsible for the observed diastereoselectivity. Would the first be true, then L,L-dipeptide isostere SAAs **2** would be directly accessible by following the same synthetic scheme, but employing *S*-*tert*-butanesulfinimide as the chiral auxiliary. In order to investigate this possibility, we prepared *S*-*tert*-butanesulfinimide **9**, the diastereoisomer of **4** with respect to the chirality at the sulfur atom. Treatment of *S*-*tert*-butanesulfinimide **9** with 3 equivalents of MeMgBr (CH_2Cl_2, −78 °C) gave a diastereoisomeric ratio for **10**–**11** of 13 : 1, as monitored by inverse gated ^{13}C NMR measurements[8] on the crude Grignard products (Scheme 1). The absolute stereochemistry of **10** was unambiguously established by acidic removal of the *S*-*tert*-butanesulfonyl group, giving, after Fmoc-protection, a compound that in all spectroscopical

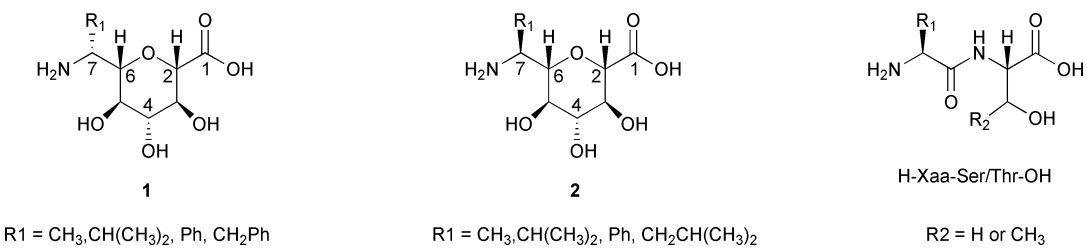
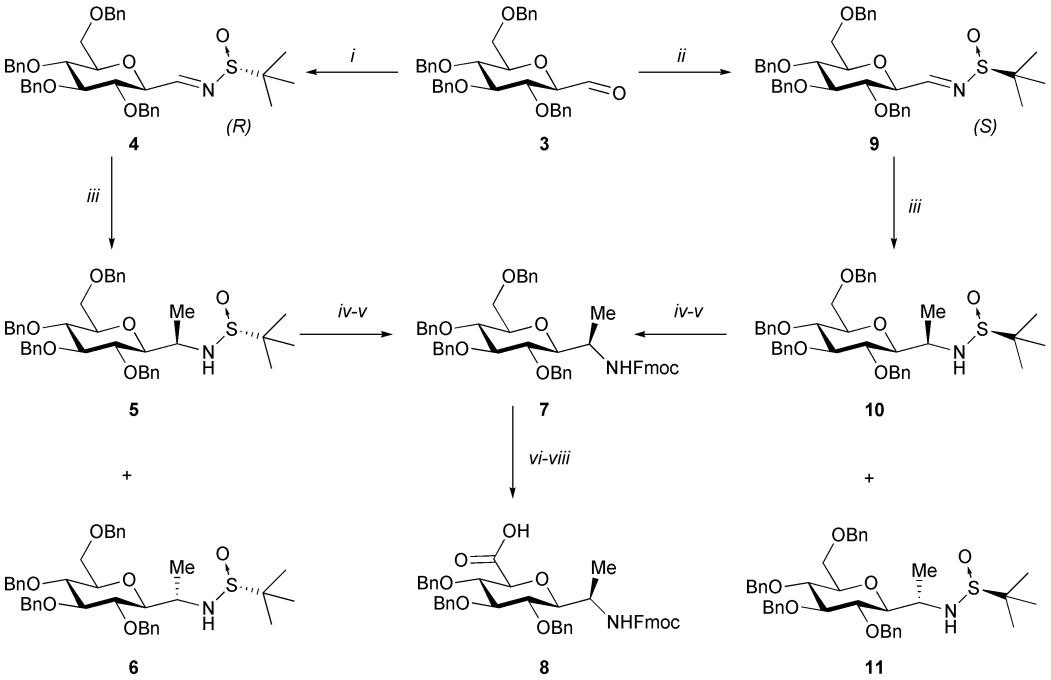


Fig. 1 Alkylated SAAs as Xaa-Ser/Thr mimics.



Scheme 1 *Reagents and conditions:* (i) *R-tert*-butanesulfinamide, $Ti(OiPr)_4$, CH_2Cl_2, 70%, (ii) *S-tert*-butanesulfinamide, $Ti(OiPr)_4$, CH_2Cl_2, 72%, (iii) MeMgBr, CH_2Cl_2 , −78 °C, (iv) HCl, MeOH, (v) FmocOSu, DIPEA, dioxane, CH_2Cl_2, (from **4**: 71%, from **9**: 75%, three steps), (vi) $ZnCl_2$, HOAc, Ac_2O, (vii) HCl, MeOH, (viii) TEMPO, BAIB, CH_2Cl_2, H_2O (64%, two steps).

aspects was identical to the previously synthesized **7** ($R^1 = CH_3$).[1] From this it follows that the minor product **11** is the *S*-methyl diastereomer of **10** with respect to the newly formed stereocentre. Apparently, *re*-side addition is favored irrespective of the nature of the chiral auxiliary on the imine nitrogen. Changing the solvent system from CH_2Cl_2 to THF resulted in a slightly more favored *si*-side addition, and **10** and **11** were formed in equal amounts. This result is the best we obtained in favor of the desired diastereoisomer **11** and we conclude that at least in this system chiral sulfinylimides are not useful intermediates in the construction of L,L-dipeptide isosteres.

At the moment we do not have a satisfying model that explains the different product ratios we observe, but it seems likely that the chelation model proposed by Ellman and co-workers in their explanation[7f] of chirality transfer (**A** to **B**, Fig. 2) is counterbalanced by competing chelation of magnesium ions to hetero-atoms on the carbohydrate template. This chelation (for instance **C**, leading to **D**) may occur irrespective of the configuration on the sulfur atom. Whether this reasoning is valid or not, it does present an obvious strategy towards the desired L,L-dipeptide isosteres. When one assumes that a formyl-*C*-glycoside chelates just as the sulfinyl imides do with magnesium and that

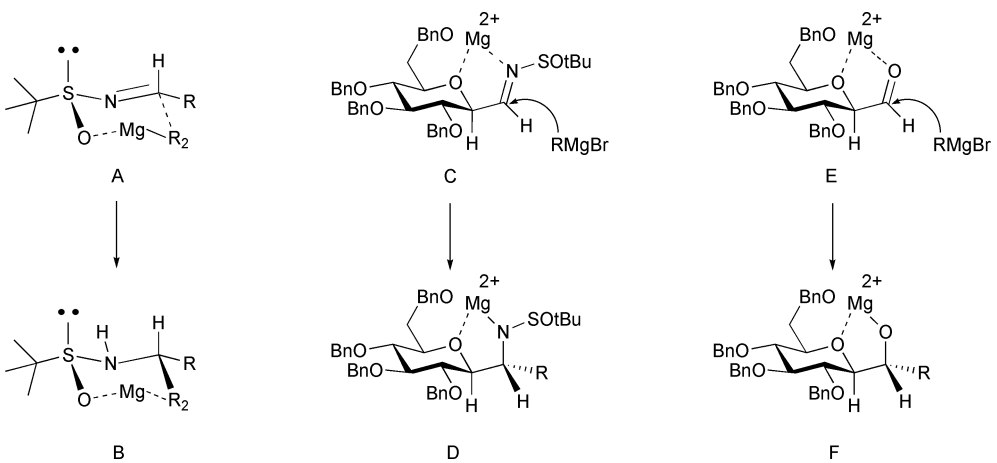


Fig. 2 Transition states for Grignard reactions (**A** → **B**: sulfinimines in general, **C** → **D**: glycosyl sulfinimide through intramolecular chelation, **E** → **F**: glycosyl aldehyde through intramolecular chelation).

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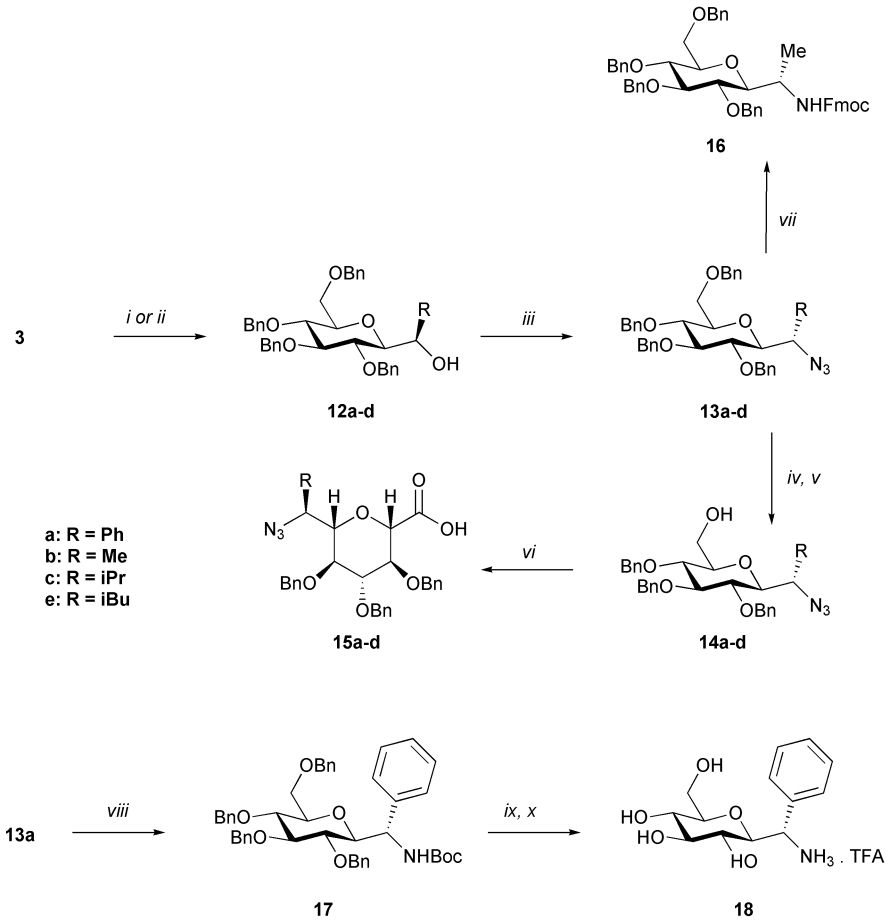

Scheme 2 *Reagents and conditions:* (i) PhMgBr, THF, −78 °C (66%), (ii) RMgBr or RMgCl, THF, 0 °C (**a** 66%; **b** 51%; **c** 36%; **d** 48%), (iii) HN_3, DEAD, PPh_3, toluene (**a** 78%; **b** 83%; **c** 48%; **d** 92%), (iv) $ZnCl_2$, HOAc, Ac_2O, (v) NaOMe, MeOH (**a** 73%; **b** 78%; **c** 68%; **d** 81%, two steps), (vi) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, H_2O (**a** 89%; **b** 91%; **c** 76%; **d** 92%), (vii) first Me_3P, THF, H_2O, then FmocCl, CH_2Cl_2–dioxane, DIPEA (73%), (viii) H_2, Lindlars catalyst, Boc_2O, MeOH (85%), (ix) Pd/C, H_2, MeOH, (x) TFA (97%, two steps).

addition occurs with the same *re*-selectivity (**E** to **F**), then the target compounds are within reach by introduction of a nitrogen substituent by replacement of the resulting alcohol function with concomitant reversal of configuration. This reasoning proved to be valid, as is outlined in Scheme 2.

Grignard addition of 3 equivalents of either PhMgBr, MeMgBr, iPrMgCl or iBuMgBr to aldehyde **3** proceeded in good diastereoselectivity to give **12a–d**, respectively, as the single isolated diastereomers in moderate to good yields (Scheme 2). The absolute configuration of the newly formed stereocentre in alcohol **12b** could be assigned as *R* since its analytical data were in excellent agreement with published values.[9] The crystals obtained from recrystallization of compound **12d** proved to be suitable for an X-ray structural determination to show the anticipated (*R*)-configuration at the newly created stereocentre.[10]

Mitsunobu displacement of the secondary alcohols **12a–d** with azide (HN_3, PPh_3, DEAD, toluene)[11] gave, with inversion of configuration, azides **13a–d**. Of these, phenylglycine analogue **13a** was transformed by a three step sequence (reduction of the azide with concomitant Boc protection yielding derivative **17** followed by hydrogenolytic cleavage of the benzylethers and TFA treatment) into known glucosylamine derivative **18**.[12] All analytical data on **18** are in agreement with those reported in the literature for the same compound hereby validating the assignment of the newly formed stereocentre in azide **13a**. The structural integrity of our compounds was further established by transformation of azide **13b** into the corresponding Fmoc-protected amide **16** (first Staudinger reduction, then treatment with fluoronylmethyloxycarbonyl chloride and DIPEA), which gave a compound with the same mass but with otherwise distinct spectroscopical properties from *R*-configured *C*-glycoside **7**. Selective acidolysis of the primary benzyl ether and subsequent oxidation of the resulting primary hydroxyls gave, after ester hydrolysis, the L,L-dipeptide isosters **15a–d**.

In conclusion, we have now at our disposal two related synthesis strategies that enable us to prepare both D,L and L,L glucopyranose derived Xaa–Ser(Thr) dipeptide isosteres. We are currently investigating their structural properties in linear and cyclic homo- and hetero-oligomers, and are pursuing adaptation of the synthesis strategy to also incorporate other functionalised amino acid side-chains.

Experimental

Full experimental procedures and physical data of the compounds described in this paper can be found in the ESI.†

Crystallography

Compound **12d** was crystallized from mixture of diethyl ether and light petroleum at room temperature as parallelepiped blocks.‡ A crystal of approximately 0.6 × 0.35 × 0.15 mm was cut from a larger one and analyzed on the Kappa CCD at 293 K using $MoK\alpha_1$ radiation. The full sphere was collected up to $\theta = 27.5°$. The data collection and processing were done using the Scalepack software.[13,14] The structure was solved by the direct method and refined using the SHELX97 package.[15] All of the non-H atoms were refined anisotropically while all H atoms were found on the Fourier Difference map and refined isotropically. The absolute configuration of the molecule was deducted knowing the absolute configurations of the four stereocentres at C2, C3, C4 and C5 as occurring in D-glucose, and the Flack parameters.[16]

Acknowledgements

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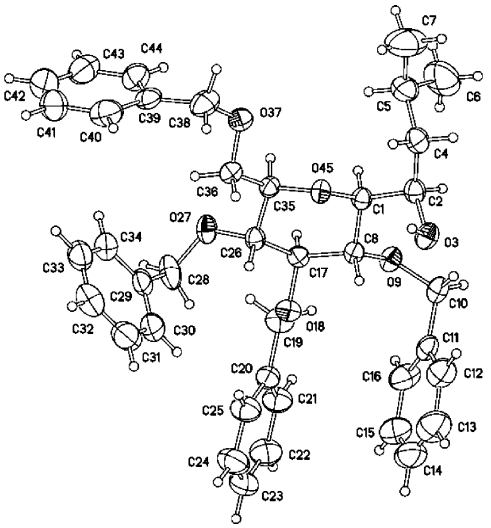

Empirical formula	$C_{39}H_{46}O_6$
Formula weight	610.76
T[K]	293(2)
λ[Å]	0.71073
Crystal system	Orthorhombic
Space group	$P\ 2_12_12_1$
Unit cell dimensions	
a [Å]	6.0520(2)
b [Å]	23.7560(5)
c [Å]	23.9440(5)
V [$Å^3$]	3442.5(2)
Z	4
D_m [g/cm^3]	1.178
Absorption coefficient mm^{-1}	0.078
F(000)	1312
Crystal size [mm^3]	0.6 x 0.3 x 0.15
θ range	3 → 27.5
Reflections collected	17437
Independent reflections	7673 [R_{int} = 0.0411]
Data / restraints / parameters	7673 / 0 / 566
S	1.025
R [I>2σ(I)]	R1 = 0.0465, wR2 = 0.0858
R indices (all data)	R1 = 0.0747, wR2 = 0.0965
Absolute structure parameter	-0.4(7)

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‡ CCDC reference number 644038. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705750d

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