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General, stereoselective synthesis of ethylene isosteres of α- and β-glycosylasparagines

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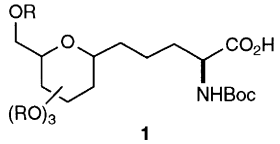
Abstract

The coupling of α- or β-D-linked lithium *C*-glycosyl acetylides with *N*-Boc D-serinal acetonide followed by the reduction of the triple bond, deoxygenation, and oxidative cleavage of the oxazolidine ring afforded α- and β-anomer pairs of *C*-glycosyl α-aminopentanoic acids (*gluco*, *manno*, *galacto*, and 2-acetamido-*galacto*).

Keywords: amino acids; *C*-glycosides; glycopeptide mimetics; *C*-glycosylasparagines; sugar acetylenes.

As potential precursors to glycopeptide mimetics,[1] *C*-glycosyl amino acids in which the glycinyl moiety is linked to the anomeric carbon of the sugar through an all carbon tether, constitute the target of recent synthetic efforts.[2] While natural glycopeptides contain *O*-glycosylserine, *O*-glycosylthreonine and *N*-glycosylasparagine units, the incorporation of *C*-glycosyl amino acids in the peptide backbone is expected to induce higher stability toward both chemical and enzymatic deglycosylation with consequential interesting biological properties. Moreover, such a simple yet substantial chemical modification may provide very useful information in studies directed at understanding the specific role of the carbohydrate moieties of glycopeptides in their properties and activities.[3] However, there is still a great need for new synthetic methods endowed with a good level of generality and allowing entry to either α- or β-linked isomers. We would like to report here a sugar acetylene approach to *N*-Boc *C*-glycosyl α-aminopentanoic acids **1**, i.e. isosteric mimetics of *N*-glycosylasparagines **2** in which the amide group has been replaced by an ethylene group. The scope of the method is documented by the preparation of the α- and β-anomer pairs of four D-pyranosides (*gluco*, *manno*, *galacto*, and 2-acetamido-*galacto*) (Table 1).



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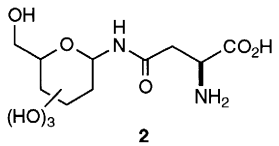

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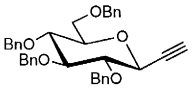
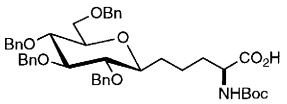
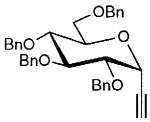
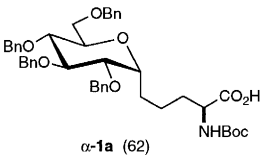
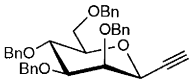
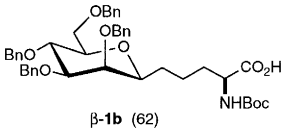
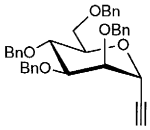
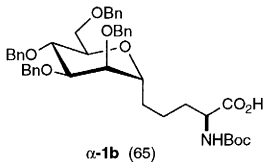
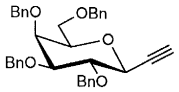
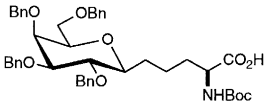
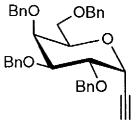
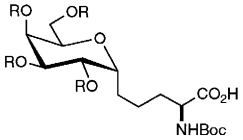
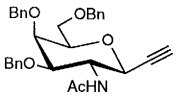
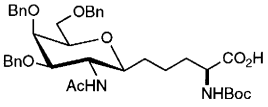
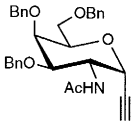
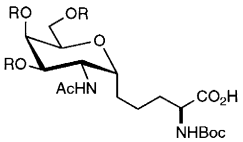
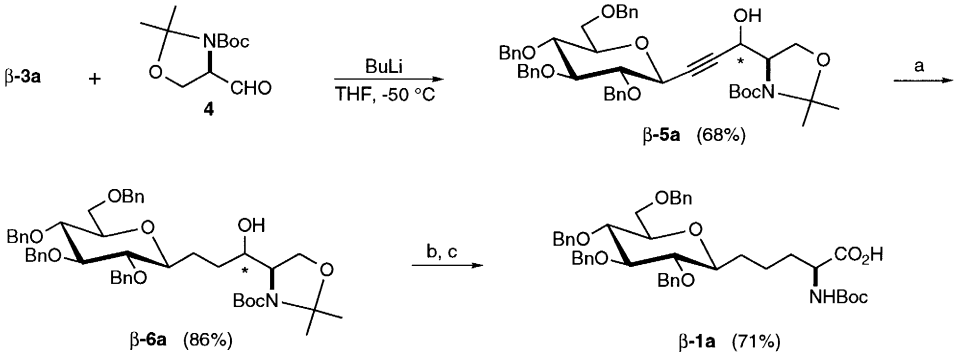
Table 1
Starting sugar acetylenes **3** and final *C*-glycosyl α-amino acids **1** prepared

acetylene, **3**	adduct, **5** (yield [%])[a]	α-amino acid, **1** (yield [%])[b]
 **β-3a**	**β-5a** (68)	 **β-1a** (61)
 **α-3a**	**α-5a** (50)	 **α-1a** (62)
 **β-3b**	**β-5b** (55)	 **β-1b** (62)
 **α-3b**	**α-5a** (45)	 **α-1b** (65)
 **β-3c**	**β-5c** (56)	 **β-1c** (56)
 **α-3c**	**α-5c** (58)	 **α-1c** R = Bn (52) **α-1c'** R = Ac
 **β-3d**	**β-5d** (75)	 **β-1d** (65)
 **α-3d**	**α-5d** (52)	 **α-1d** R = Bn (38) **α-1d'** R = Ac

[a] Yields of isolated adduct **5** by coupling the acetylene sugar **3** with **4**. [b] Yields of isolated compounds **1** from the adducts **5**.

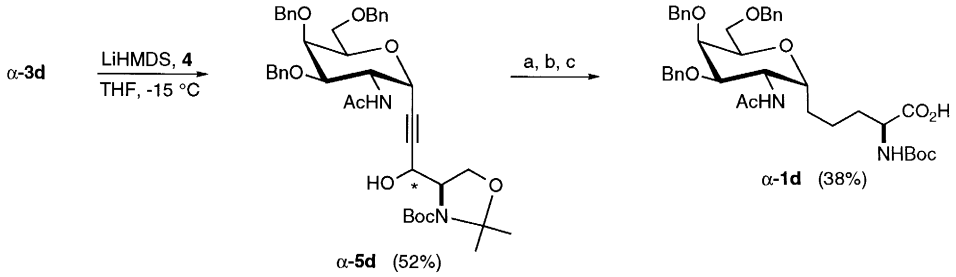
While sugar acetylenes are receiving increasing attention as building blocks in carbohydrate chemistry,[4] the reaction of their metalated derivatives with aldehydes has not been reported so far. Thus, we were delighted to observe that the model reaction generated by addition of the lithium acetylide derivative[5] β-**3a** of the tetra-*O*-benzyl-*C*-glucopyranoside to the protected D-serinal **4** proceeded readily at low temperature to give the propargylic alcohol β-**5a** in good isolated chemical yield (Scheme 1).[9] This compound appeared to be a single diastereomer as judged by ^{1}H NMR analysis, very likely with (*S*) configuration at the newly formed stereocenter (*anti* adduct).[12] Suitable and high yielding reactions were employed for the elaboration of the side chain of the *C*-glucoside β-**5a**. First, the triple bond was reduced by the use of diimide generated in situ from (*p*-toluenesulfonyl)hydrazine and sodium acetate. The saturated alcohol β-**6a** was deoxygenated by the standard Barton–McCombie method and the oxazolidine ring was cleaved and oxidized in one pot by use of the Jones reagent as described in recent work conducted in this laboratory.[2a] The resulting *C*-glucosyl α-aminopentanoic acid β-**1a** was isolated in 61% overall yield from the adduct β-**5a** and was characterized as its methyl ester.[9] This product showed consistent NMR and optical rotation data with that of the product prepared by us by a previous route.[2a] An identical reaction scheme was followed for the preparation[9] of the anomer α-**1a** as well as the *C*-mannosyl pair α-**1b** and β-**1b** and the *C*-galactosyl pair α-**1c** and β-**1c** starting from the corresponding *O*-benzylated sugar acetylenes[5] (Table 1). The yields of isolated intermediates and final products were comparable to those registered in Scheme 1.



Scheme 1. Synthesis of the glucosylasparagine isostere β-Glc(CH_2)$_2$-Asn β-**1a**. *Reagents and conditions*: (a) $TsNHNH_2$, AcONa, DME–H_2O, 80°C, 5 h; (b) 1,1′-thiocarbonyldiimidazole, DMAP, THF, reflux, 4 h; Bu_3SnH, AIBN, toluene, 85°C, 2 h; (c) 1 M Jones reagent, acetone, 0°C to rt, 3 h

The *C*-Gal*N*Ac derivatives β-**1d** and α-**1d** were obtained[9] in a similar way, and in comparable yields to those above, starting from the dilithio derivative of the corresponding 2-acetamido sugar acetylenes[5] β-**3d** and α-**3d**. The synthesis of the α-linked isomer α-**1d** is presented in Scheme 2. It is worth noting that an alternative synthetic approach to this compound by the use of the lithium acetylide derivative of the azidosugar was hampered by the very low yields (5%) of the coupling reaction with the aldehyde **4**. Instead, unstable products, very likely cycloadducts of the azido group to the ethynyl moiety, were observed which decomposed during the workup of the reaction mixture. Reactions of the azido group with adjacent unsaturated centres linked to the anomeric carbon of sugars have been reported.[13]

In summary, centered on the coupling of two chiral building blocks, i.e. sugar acetylenes and a protected α-amino aldehyde, a new route has been paved to *C*-glycosyl amino acids that are ethylene isosteres of *N*-glycosylasparagines. The method appears to be suitable for the preparation of α- and β-D-linked anomers of various sugars including 2-deoxy-2-acetamido derivatives that are of special biological relevance. The method exploits the stereochemistry already in place at the anomeric carbon of sugar acetylenes that provide part of the carbon tether while the oxazolidine ring of the aldehyde **4** serves



Scheme 2. Synthesis of the 2-acetamido-galactosylasparagine isostere α-Gal*N*Ac$(CH_2)_2$-Asn α-**1d**. Reagents and conditions as in Scheme 1

as the protected and configurationally stable glycinyl moiety.[2a] Finally, the *O*-benzylated compounds α-**1c** and α-**1d** were transformed into the corresponding *O*-acetylated derivatives α-**1c**′ and α-**1d**′ by debenzylation (H_2, $Pd(OH)_2$, rt, 2 h) and acetylation (Ac_2O, Py, rt, 4 h). This simple yet important transformation demonstrated that the products of this synthetic approach are orthogonally protected and therefore can be easily converted into suitable building blocks for the incorporation within large peptide frameworks.

Acknowledgements

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(*c* 0.8). Compound α-**3c**: [α]=+31.1 (*c* 1.7). Compound β-**3d**: m.p. 174–176°C (AcOEt–cyclohexane); [α]=+36.1 (*c* 0.9). Compound α-**3d**: m.p. 143–145°C (cyclohexane); [α]=+95.9 (*c* 0.9). Compound β-**1a** Me-ester: [α]=+6.2 (*c* 0.7). Compound α-**1a** Me-ester: m.p. 79–81°C (pentane); [α]=+36.5 (*c* 1.5). Compound α-**1b** Me-ester: [α]=+22.6 (*c* 0.8). Compound β-**1b** Me-ester: [α]=+5.5 (*c* 0.6). Compound α-**1c** Me-ester: [α]=+26.5 (*c* 0.6). Compound β-**1c** Me-ester: [α]=+6.4 (*c* 0.5). Compound α-**1c**′ Me-ester: [α]=+60.0 (*c* 0.6). Compound β-**1d** Me-ester: [α]=+27.0 (*c* 0.6). Compound α-**1d** Me-ester: [α]=+23.3 (*c* 1.2). Compound α-**1d**′ Me-ester: [α]=+46.3 (*c* 0.5).

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