Stereoselective *α*-Glycosylation using fluorinated linker

Dr. Sharavathi G. Parameswarappa (PQ),[1] Dr. Benjamin Schumann (PG),[1,2] Dr. Marilda P. Lisboa (PQ),[1] Dr. Naresh Kottari (PQ),[1] Fabio Guidetti (IC),[1] Dr. Claney L. Pereira (PQ),[1] Prof. Dr. Peter H. Seeberger* (PQ)[1,2]

[1]Department of Biomolecular Systems, Max Planck Institute of Colloids and Interfaces; [2]Institute of Chemistry and Biochemistry, Free University of Berlin

***peter.seeberger@mpikg.mpg.de**

[1]Am Mühlenberg 1 - 14476 Potsdam, Germany; [2]Arnimallee 22-14195 Berlin, Germany

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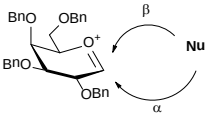
Abstract

In the development of synthetic carbohydrate vaccines a linker is installed in the reducing end of the sugar unit. The linker is used to facilitate the printing of glycan microarrays and for conjugation with carrier proteins. One of the key challenges in carbohydrate synthesis is the stereoselective formation of 1,2-*cis* glycosidic bonds with linkers.[1] Herein, we report an easily accessible difluorinated-alcohol linker that gives high α-selective glycosylation involving various glycosyl donors. The low nucleophilicity of the linker acceptor is likely to account for the stereoselectivity observed.[2] Experimental studies to evaluate the effect of different solvents, temperature and activators were performed. Computational studies to explain the stereoselectivity of glycosylation with fluorinated linker are currently underway.

Introdução

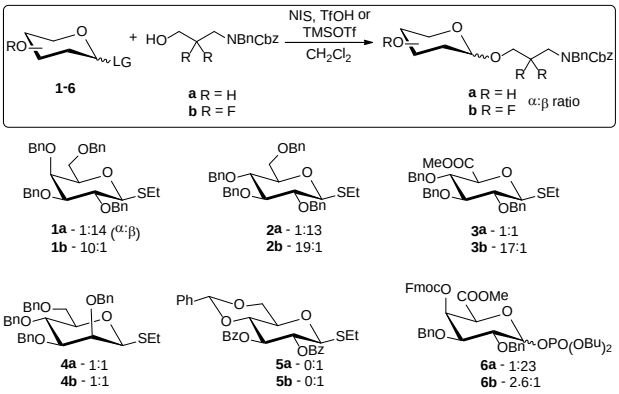
Our group is interested in the development of synthetic carbohydrate vaccines.[3] One of the challenges during the synthesis of such antigens is the selective installation of an alkyl linker at the reducing end of the sugar. Woerpel reported that glycosylation using trifluoroethanol as acceptor gave preferentially 1,2-*cis* glycosides.[2] Based on this observation, a difluorinated linker was designed and the steroselectivity investigated.



Resultados e Discussão

The fluorinated linker was synthesized in four steps from diethyl 2,2-difluoromalonate. Non-fluorinated and fluorinated linkers (**a**,**b**) were used as acceptors in the glycosylation with various donors (Figure 1). For the galactose substrate **1** with thioglycoside donor, glycosylation with non-fluorinated linker gave mainly the beta anomer (*α*:*β* ratio 1:14). However, using the fluorinated linker the selectivity was inverted to 10:1 (*α*:*β*). The same trend was observed for other substrates including glucose, glucuronic acid and galactose with phosphate donors (**2**, **3** and **6**). Stereoselectivity was not observed for mannose (**4**). It was pleasing to observe that the fluorinated linker did not overcome the effect of the benzoyl participating group at C-2 (**5**). Additionally, the effect of the solvent, temperature and activators were investigated. Solvent mixtures like DCM/Et_2O and toluene/dioxane improved the formation of *cis* glycosides. Milder activators and temperature affected stereoselectivity as well. The presence of the fluorine atoms decrease the nucleophilicity of the acceptor, lowering the HOMO and favoring one of the products. Further computational experiments are being performed to explain the preference for the nucleophilic attack at the bottom face of the pyranoside ring in the oxocarbenium ion.

Figure 1. Selectivity using different glycosyl donors.



Conclusões

Herein, we report a designed fluorinated linker that showed high *α*-stereoselectivity in the reaction with various glycosyl donors. Temperature, solvent and activators also play a role in the stereoselectivity.

Agradecimentos

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