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Conformationally restricted 3,5-*O*-(di-*tert*-butylsilylene)-D-galactofuranosyl thioglycoside donor for 1,2-*cis* α-D-galactofuranosylation

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ABSTRACT

A conformationally restricted 2-*O*-benzyl-3,5-*O*-di-*tert*-butylsilylene-β-D-thiogalactofuranoside donor was prepared from benzyl α-D-galactofuranoside and its donor capability was studied for stereoselective 1,2-*cis* α-D-galactofuranosylation. An unusual chemical behavior in benzylation and hydrogenolysis reactions was observed after the introduction of the 3,5-*O*-di-*tert*-butylsilylene protecting group into the galactofuranosyl moiety. The influence of the solvent, temperature, and activating system was evaluated. The NIS/AgOTf system, widely used in 1,2-*cis* β-arabinofuranosylation, was not satisfactory enough for 1,2-*cis* galactofuranosylation. However, moderate to high α-selectivity was obtained with all the acceptors employed when using *p*-NO_2PhSCl/AgOTf as a promoting system, in CH_2Cl_2 at −78 °C. The order of the addition of the reactants (premixing or preactivation) did not affect substantially the stereochemical course of the glycosylation reaction. The α-D-Gal*f*-(1→6)-D-Man linkage was achieved with complete diastereoselectivity by preactivation of the conformationally constrained thioglycoside donor.

1. Introduction

Galactofuranose-containing oligosaccharides have attracted much attention because Gal*f* is not found in mammals whereas it is a common constituent in pathogenic microorganisms such as *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, and *Klebsiella pneumoniae*.[1–3] Interestingly, Gal*f* is found in β-configuration in all cases. For that reason, Gal*f* metabolism has been proposed as a potential target for chemotherapy,[4] and in this context, studies on its biosynthesis are currently being performed.[2,5,6] Although not so widely distributed, α-D-Gal*f* in 1,2-*cis* configuration has also been found in several pathogenic bacteria such as *Escherichia coli* O167[7] and O85,[8] *Salmonella enterica* O53[9] and O17,[8] *Pragia fontium*,[10] *Streptococcus pneumonia* 22F,[11] and pathogenic fungi such as *Paracoccidioides brasiliensis*,[12] and others.[1,13] The biosynthetic pathway of this unit as well as its metabolism is still unknown. Stereoselective methods for the synthesis of α-D-Gal*f*-containing oligosaccharides are of great interest bearing in mind that the availability of these derivatives will allow to perform further biological assays.

The glycosylation reaction involves too many factors and, at the present time, is an intense and relevant area of research.[14–18] In fact, studies on stereoselective furanosylation are more limited compared to pyranosides,[16,19] in which the 1,2-*cis* β-*manno* type glycosidic linkage and α-2-deoxypyranoside linkage are the most difficult to achieve stereoselectively.[16] The complexity for constructing 1,2-*cis* α-D-Gal*f* linkages could be compared to stereochemically related 1,2-*cis* β-arabinofuranosyl linkage which has been extensively studied[20–23] probably due to its presence in the *M. tuberculosis* arabinogalactan and lipoarabinomannan.[24] No general method for α-D-galactofuranosylation as a single diastereomer has been accomplished yet.[1,2] A strong influence of the acceptor has been usually observed by the use of tetrabenzylated galactofuranosyl donors such as trichloroacetimidates[25–28] or thioglycosides.[29] Recently, the preparation of a α-D-Gal*f* glycolipid analog was described by the Lemieux-type halide ion-catalyzed glycosylation with a high α/β diastereomeric ratio and a moderate yield.[30] A complete stereoselective α-D-galactofuranosylation was first described employing a tetrabenzylated carboxybenzyl galactofuranoside in the synthesis of agelagalastatin.[31] Presumably, a S_N2-type displacement of a α-triflate intermediate is involved. It is worthy to point out that a tetrabenzylated substitution on the donor was a requirement for a complete control of the stereochemistry in the construction of the terminal α-D-Gal*f*-(1–2)-D-Man linkage.[32] The 2,3-anhydrosugar methodology was also used in α-D-galactofuranosylation. In this indirect method, a complete diastereoselection was achieved in the glycosylation reaction but not

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in the subsequent epoxide ring opening.[33,34] The intramolecular aglycon delivery strategy is an interesting example that was successfully employed in the synthesis of a 1,2-*cis* α-D-fucofuranoside, a 6-deoxy analogue of α-D-galactofuranose.[35] More recently, a complete stereoselective formation of the α-D-Gal*f*(1→2)Rha linkage in the synthesis of a trisaccharide constituent of *Streptococcus pneumoniae* 22F was carried out by the trichloroacetimidate method, after tuning the reactivity of the galactofuranosyl donor and the rhamnoside acceptor.[36]

The less pronounced anomeric effect and the flexible ring of furanose increase the difficulty to obtain 1,2-*cis* linkages stereoselectively. Inspired by studies on *C*-glycosylation of five-membered ring oxacarbenium ions performed by Woerpel et al.,[37] 3,5-*O*-di-*tert*-butylsilylene[21,22] and 3,5-*O*-tetra-isopropyldisiloxanyllidene[23] conformationally locked arabinofuranoside donors were developed to avoid the eclipsing interaction between the incoming nucleophile acceptor and H-2 of the oxacarbenium ion in the presumably E_3 conformation,[21] leading to 1,2-*cis* glycosides with high diastereoselectivity. The development of these donors[21–23,38–40] (Fig. 1) allowed the synthesis of relevant β-arabinofuranoside-containing oligosaccharides found in nature.[21,23,39–43] The conformationally restricted 2,3-*O*-xylylene-protected Ara*f* thioglycoside donor was also developed allowing the synthesis of an oligosaccharide fragment of mannose-capped mycobacterial lipoarabinomannan.[44]

Focusing on 3,5-*O*-di-*tert*-butyl-silylene protection in β-arabinofuranosylation, several methods of glycosylation proved to be highly β-selective among several acceptors, which includes the extensively studied thioglycoside,[21,22,38–41] sulfoxide,[22] and trichloroacetimidate[38,39] method (Fig. 1). A complete β-diastereoselectivity was observed using the conformationally constrained trichloroacetimidate donor L-**5** in the synthesis of a hexasaccharide and related fragments of plant cell wall-constituent rhamnogalacturonan II, whereas a slightly reduced anomeric selectivity was obtained employing the 1-thioarabinofuranoside analog L-**2**.[39]

In view of these results, conformationally restricted 3,5-*O*-(di-*tert*-butylsilylene)-D-galactofuranosyl trichloroacetimidate donors **9** and **10**[45] (Fig. 2) have been evaluated for 1,2-*cis* α-galactofuranosylation aimed at favoring the entrance of the nucleophile acceptor from the inside α-face in the presumed E_3 oxacarbenium intermediate (Fig. 2) avoiding the eclipsing interaction with H-2 in the β-face trajectory. Unexpectedly, and contrary to it was depicted the case of the arabinofuranosyl counterpart, almost no 1,2-*cis* α-selectivity was observed when employing the non-participating solvent CH_2Cl_2.[45] On the other hand, modest to high selectivity was observed using diethylether as solvent at −78 °C, suggesting a participating effect on the intermediate.[45] Interestingly, the opposite situation had been observed with the flexible analogous, trichloroacetimidate 2,3,5,6-tetra-*O*-benzyl-β-D-galactofuranoside (**11**, Fig. 2) in which ethereal solvents gave no selectivity or slightly favored the β product, whereas CH_2Cl_2 favored the 1,2-*cis* α-product.[28]

Moreover, higher α-selectivity was obtained with 6-*O*-acetyl substituted constrained trichloroacetimidate donor **9** rather than 6-*O*-benzyl analogue **10** which excludes a remote participation

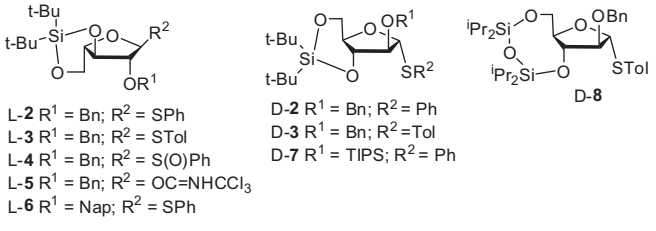

Figure 1. Examples of conformationally constrained donors used for 1,2-*cis* β-Ara*f* linkage construction.

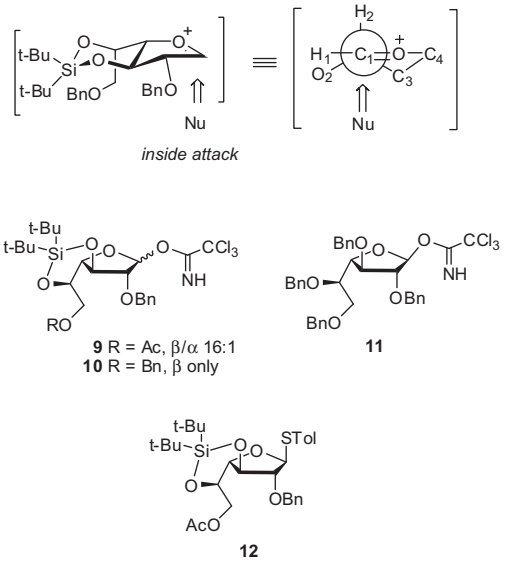

Figure 2.

effect and it suggests its involvement in a stereoelectronic effect due to the presence of an electron withdrawing group.[45]

Taking into consideration the fact that selectivity is affected by the glycosylation method as well as the promoter used, as it was demonstrated in the thioarabinofuranosyl counterpart by Crich et al.,[22] we decided to investigate the conformationally restricted thioglycoside **12**, which is the analogue of trichloroacetimidate **9** (Fig. 2).

In this article, we describe the synthesis of *p*-tolyl 6-*O*-acetyl-2-*O*-benzyl-3,5-*O*-(di-*tert*-butylsilanediyl)-1-thio-β-D-galactofuranoside (**12**) and we discuss its ability as a donor in the glycosylation reaction, its scope, and its limitation.

2. Results and discussion

The synthesis of galactofuranosyl derivatives involves the selection of the corresponding galactofuranosyl precursor. In this case, at first sight, the employment of a thiogalactofuranoside as starting material was evident. At the beginning, we selected *p*-tolyl 1-thio-β-D-galactofuranoside[46] (**13**) aimed at following a similar reaction sequence performed by us in the synthesis of conformationally locked imidate **9**.[45] This sequence would involve regioselective 2,6-di-O-benzoylation of **13** and further 3,5-*O*-di-*tert*-butylsilylene incorporation. For that purpose, selective 2,6-di-O-benzoylation was first attempted by treatment of **13** with 2.2 equiv of benzoyl chloride at −15 °C. However, a complex mixture of products was obtained which included 6-*O*-, 5,6-di-*O*-, 2,6-di-*O*-, and 3,6-di-*O*-benzoyl thiotolylgalactofuranosyl derivatives. Selective pivaloylation of **13** at −15 °C was also attempted but a complex mixture was obtained once again despite the bulky protecting group. These results were in agreement with those previously described that showed the selective benzoylation of *p*-tolyl 5,6-*O*-isopropylidene-1-thio-β-D-galactofuranoside by treatment with benzoyl chloride (1 equiv) to lead to 2-*O* and 3-*O* derivatives in 45% and 26% yield, respectively.[47] Moreover, protection with the bulky silylating agent *tert*-butyldimethylsilyl chloride gave the 2-*O*-silyl derivative in 60% yield together with 3-O-derivative in 12% yield.[48] Clearly, thiogalactofuranoside **13** was not a convenient starting material since the difficulty exhibited to protect selectively the 2-OH position by direct acylation. For that reason, it was decided to incorporate the thiocresyl moiety in a later stage, that is, once the 3,5-*O*-DTBS has been introduced (Fig. 3).