Carbohydrate Research 345 (2010) 385–396

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of trisaccharides containing internal galactofuranose O-linked in *Trypanosoma cruzi* mucins

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ARTICLE INFO

Article history:
Received 21 October 2009
Received in revised form 24 November 2009
Accepted 5 December 2009
Available online 14 December 2009

Keywords:
Trypanosoma cruzi
Mucin
Trisaccharide
Trichloroacetimidate glycosylation
Galactofuranose
Galactonolactone

ABSTRACT

The trisaccharides β-D-Gal*f*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNAc (**5**) and β-D-Gal*p*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNAc (**6**) constitute novel structures isolated as alditols when released by reductive β-elimination from mucins of *Trypanosoma cruzi* (Tulahuen strain). Trisaccharides **5** and **6** were synthesized employing the aldonolactone approach. Thus, a convenient D-galactono-1,4-lactone derivative was used for the introduction of the internal galactofuranose and the trichloroacetimidate method was employed for glycosylation reactions. Due to the lack of anchimeric assistance on O-2 of the galactofuranosyl precursor, glycosylation studies were performed under different conditions. The nature of the solvent strongly determined the stereochemical course of the glycosylation reactions when the galactofuranosyl donor was substituted either by 2-*O*-Gal*p* or 2-*O*-Gal*f*.

1. Introduction

Trypanosoma cruzi, the agent of Chagas' disease, the American trypanosomiasis, presents a surface dominated by carbohydrates.[1,2] The mucins of *T. cruzi* stand out, not only because of their crucial function but also from the structural point of view. They are acceptors of sialic acid in the well-studied trans-sialidase reaction,[3–5] closely related to the infectivity of the parasite. A puzzling fact is that the presence of galactofuranose is confined to strains of a sylvatic origin grouped as *T. cruzi* I[6] (Fig. 1). These are less infective than strains belonging to group II, from the domestic cycle,[7] that only contain galactopyranose. The oligosaccharides **1**–**4** and **8** (Fig. 1) were first described in mucins of the G-strain.[8,9] They present a unique core of β-D-Gal*f*-(1→4)-GlcNAc which is α-*O*-glycosidically linked to serine or threonine in the mucins. Later, the same structures were found in the Dm28c clon together with the novel oligosaccharide **7**.[10] More recently, in the Tulahuen strain, trisaccharides **5** and **6** as well as pentasaccharide **9** were also found.[6] In 2009, from drug-resistant Colombiana strain, isolated from a chronic human case in Colombia, oligosaccharides **1**–**4** and **8**, as in the G-strain, were found.[11] Among these oligosaccharides, **5**–**9**, present an internal Gal*f*, 2-O-substituted by Gal*p* or Gal*f*. Our laboratory has been involved in the synthesis of this family of compounds with the aim to use them for trans-sialidase studies.[12] To date, we have reported the synthesis of compounds **1**–**4** (Fig. 1).[13–16] Pentasaccharide **4**, the major oligosaccharide in the G-strain, has two terminal Gal*p* for possible sialylation. By preparative trans-sialylation of **4** and analysis of the product, we have demonstrated that selective monosialylation occurs on the (1→3)-linked Gal*p*.[16] Recently, the synthesis of a mucin oligosaccharide from the Y strain (group II), which lacks Gal*f*, has been also reported.[17]

In this work, we describe the synthesis of β-D-Gal*f*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNAc (**5**) and β-D-Gal*p*-(1→2)-β-D-Gal*f*-(1→4)-D-GlcNAc (**6**) and the corresponding alditols, employing the aldonolactone approach. Trisaccharide **5** is part of the higher oligosaccharides **7** and **9**, whereas trisaccharide **6** is included in **8**. Thus, intermediates of these syntheses are useful for the construction of the higher oligosaccharides. The two linear trisaccharides present an internal galactofuranose unit substituted at position 2 by β-Gal*f* or β-Gal*p*. Thus, stereoselective glycosidation was hampered by the lack of neighboring group assistance.

The biosynthetic pathways involved in the construction of these O-chains in the mucins have not been elucidated. Taking into account the various structures found in *T. cruzi*, the synthesis of these oligosaccharides would be useful for studies on their biosynthesis.

2. Results and discussion

The synthesis of Gal*f* containing oligosaccharides from other glycoconjugates of *T. cruzi* has been performed; however, in these cases, Gal*f* appeared as terminal non-reducing end.[18,19] The synthesis of oligosaccharides containing internal galactofuranose is

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0008-6215/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2009.12.005

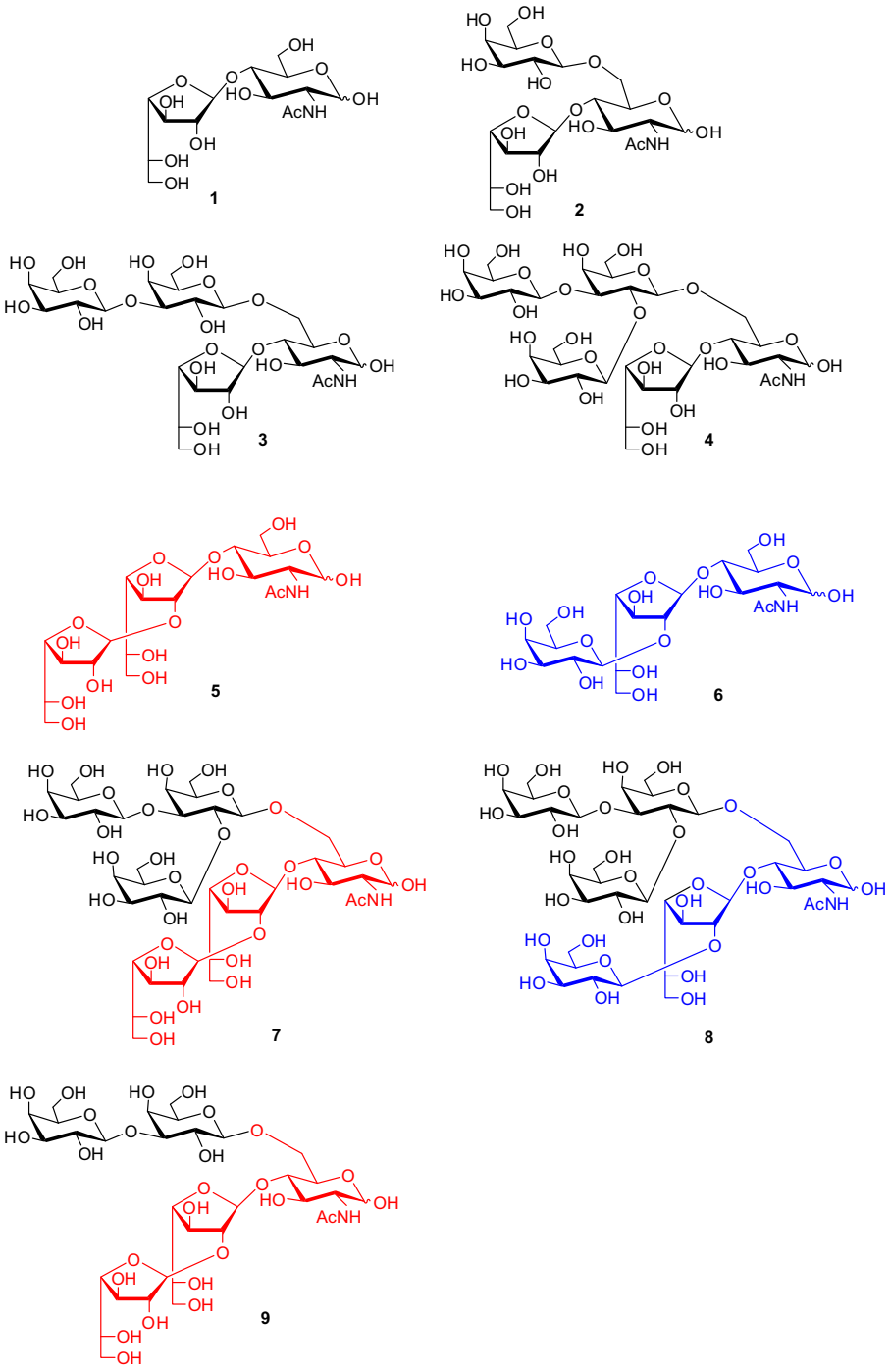

Figure 1. Oligosaccharides in mucins of *Trypanosoma cruzi* (group I).

more challenging, and involves the choice of convenient galactofuranosyl precursors as well as glycosylation methods. These aspects have been recently reviewed.[20,21] Few internal β-Gal*f* containing oligosaccharides have been synthesized to date.[22–29] The following methods were employed for the internal linkage construction: Koenings–Knörr,[22a] cyanoorthoester,[22b–d] anomeric acetate,[23] trichloroacetimidate,[24–26] and more recently, thioglycoside,[27] 2′-carboxybenzyl-glycosides[28,29] and glycosyl fluoride.[29]

Our strategy relied on the use of a convenient derivative of D-galactono-1,4-lactone as a common precursor of the internal Gal*f* of both trisaccharides, **5** and **6**. The glycosyl aldonolactone approach has been employed for the syntheses of a trisaccharide present in glycoinositolphospholipids from *Leishmania*[24] and oligosaccharide constituents of the arabinogalactan from *Mycobacterium tuberculosis*.[25] The stable lactone acts as a virtual-protected Gal*f* and may be also selectively substituted,[30,31] avoiding the tedious synthesis of the Gal*f* unit precursor from galactose, thus, providing a straightforward method for the oligosaccharide synthesis. On the other hand, in our previous work related to mucin oligosaccharides,[15,16] we have succeeded in glycosylating the 4-OH of GlcNAc derivative, benzyl 2-acetamido-3-*O*-benzoyl-6-*O*-*t*-butyldiphenylsilyl-2-deoxy-α-D-glucopyranoside (**18**) with a galactofuranosyl imidate donor with very good yield. For that reason, we decided to use the same derivative **18** considering, in addition, that