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Carbohydrate Research 342 (2007) 894–900
Carbohydrate RESEARCH

α and β L-Fucopyranosyl oxyamines: key intermediates for the preparation of fucose-containing glycoconjugates by oxime ligation

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Received 15 November 2006; received in revised form 15 January 2007; accepted 4 February 2007
Available online 12 February 2007

Abstract—We report herein the synthesis of new α and β aminooxylated L-fucopyranosyl derivatives for the preparation of glycoclusters through oxime ligation. The glycosylation reaction between activated triacetylated L-fucopyranosyl fluoride and *N*-hydroxyphthalimide was carried out in the presence of boron trifluoride–diethyl etherate and the stereochemical outcome of glycosylation was compared in dichloromethane, acetonitrile or tetrahydrofuran. Interestingly, an unexpected α and β anomer ratio was obtained in spite of the presence of an acetate participating group at the carbon 2, particularly the 1,2-*cis* glycosylation was largely favoured in acetonitrile. The resulting α and β *N*-oxyphthalimido fucopyranosyl derivatives were finally deprotected with methylhydrazine to obtain the corresponding free aminooxylated fucopyranosyls. The structure of single-crystal α anomer **12** was analysed by X-ray diffraction.

Keywords: Aminoxylated fucopyranosyl; Glycosylation; Anomeric mixture; Oxime ligation; Crystal structure; Glycocluster

1. Introduction

As part of our programme to develop new chemical tools for glycomics,[1–3] we focussed recently our synthetic efforts on the L-fucose motif which is a relevant part of ligands involved in a wide range of biological processes.[4,5] In mammals, fucose-containing glycans play a crucial role in the recognition events related to fertilisation, development or adhesion of leukocytes to vascular endothelial cells, which is mediated by interactions between selectin and glycans at the initial state of inflammation processes.[6] Moreover, fucosylated glycoconjugates are involved in many diseases, going from pathogen infections[7] to cancers.[8] For example, it has recently been shown that the chronic colonisation of the lung with *Pseudomonas aeruginosa*, which is responsible for infections in patients affected with cystic fibrosis, starts with the adhesion of the bacterium to the host cells through fucose-binding PA-IIL lectin present at its surface.[9]

Inhibiting these host/pathogen recognition processes, which occur mostly through multivalent interactions, might efficiently prevent infections. For this purpose, the synthesis of glycoclusters appears as one of the most promising approaches to discover new active and selective therapeutics.[10] Among the very large panel of reported synthetic methods, chemoselective ligations have emerged as an attractive strategy for the assembly of biomolecules.[11,12] In our laboratory, we have chosen chemoselective oxime bond formation to prepare cyclic decapeptides exhibiting clusters of carbohydrates in solution as well as on solid support for diagnostic or therapeutic applications.[1–3] Our oxime-based strategy relies on the convergent assembly of aminooxylated carbohydrates onto templates presenting aldehyde functions. Herein, we report the synthesis of new fucopyranosyl derivatives **12** and **13** bearing at the anomeric centre both α and β aminooxy functionalities that are essential for the evaluation of the influence of anomeric configurations on recognition (Fig. 1). These derivatives represent key intermediates for further assembly onto scaffolds to form clusters and evaluation

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doi:10.1016/j.carres.2007.02.003

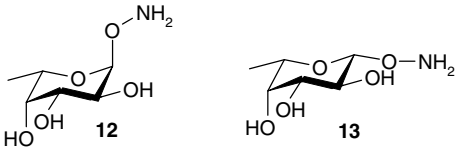


Figure 1. Structure of aminooxylated α and β L-fucopyranosyl **12** and **13**.

of the resulting fucose-containing conjugate as anti-infective agents.

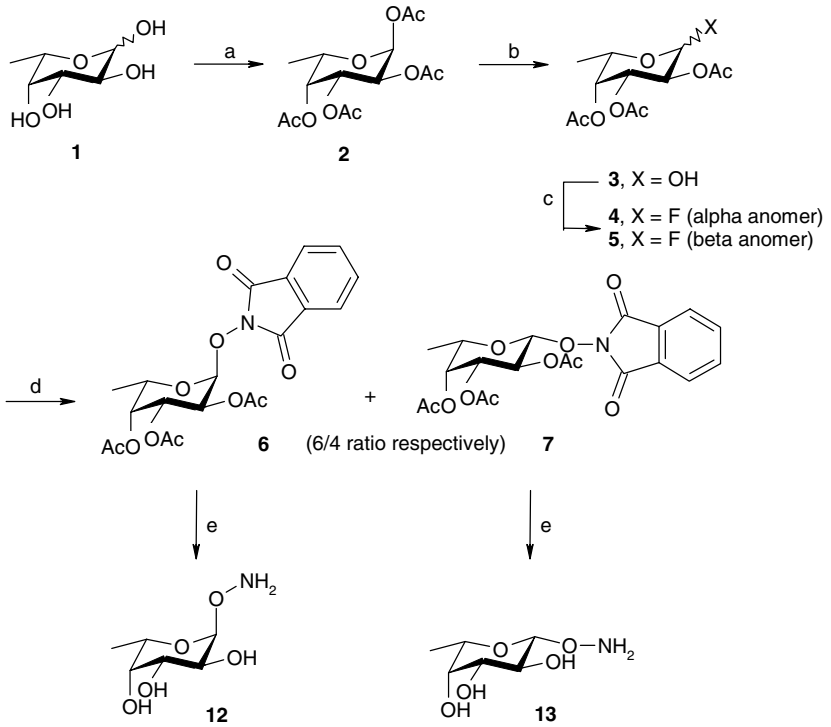
2. Results and discussion

2.1. Synthesis

We reported previously a general method for the preparation of aminooxylated carbohydrate-based ligands[13] and cancer-related antigens[14] using a glycosylation reaction between glycosyl fluoride donors and *N*-hydroxyphthalimide as the key step. This efficient synthetic strategy has been applied to the L-fucose series to prepare the corresponding aminooxylated derivatives (Scheme 1). The commercial L-fucopyranose **1** was first protected with acetates in the presence of pyridine and acetic anhydride. The peracetylated compound **2** was then deprotected regioselectively at the anomeric position by treatment with a solution of ethylenediamine/acetic acid (1/1)[15] in tetrahydrofuran to obtain **3** in 86% yield. A fluoride was introduced as an anomeric leaving group to the triacetylated fucopyranose **3** by using diethylaminosulfur trifluoride (DAST) in THF.[16] The fluorinated compound has been obtained as an α/β anomer mixture (1.2/1, 72% yield).

When the glycosylation reaction was carried out between crude anomer mixture **4/5** and *N*-hydroxyphthalimide in the presence of triethylamine and boron trifluoride–diethyl etherate ($BF_3{\cdot}Et_2O$)[17] as promoter in dichloromethane (Scheme 1), both the α and β fucopyranosyl-*N*-oxyphthalimide anomers **6** and **7** were formed and purified by silica gel chromatography and recrystallisation. They were characterised by using electrospray ionisation mass spectrometry and ^1H, ^{13}C and 2D (GCOSY and GHMQC) NMR experiments. The determination of the coupling constant (*J*) between protons H-1 and H-2 was in good agreement with the anomer configuration of **6** ($J_{1,2} = 4.0$ Hz) and **7** ($J_{1,2} = 8.1$ Hz). Interestingly, this glycosylation gave a poor anomeric ratio in favour of the α anomer (α/β = 1.5/1). While it is well established that the presence of an ester protecting group at C-2 enables the preferential formation of a 1,2-*trans* glycosidic linkage due to the assistance of a neighbouring participating group,[18–20] this result indicates a minor influence of the acetate on the stereoselectivity of this reaction.

Several publications report unexpected stereochemical outcomes for glycosylation. For example, it has been



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, 6 h, 97; (b) ethylenediamine, AcOH, THF, 12 h, 86%; (c) diethylaminosulfur trifluoride, THF, 1 h, 72% (α/β anomer, 1.2/1); (d) *N*-hydroxyphthalimide, $BF_3{\cdot}Et_2O$, Et_3N, dry CH_2Cl_2, 1 h, 77%; (e) $MeHNNH_2$, EtOH, 12 h, 51%.