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Synthesis of a C-linked hyaluronic acid disaccharide mimetic

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Abstract—The synthesis of a C-disaccharide that is designed as a mimetic for the repeating unit disaccharide of hyaluronic acid is described. The target compound was obtained via the SmI_2-promoted coupling reaction of the sulfone, 2-acetamido-4,6-*O*-benzylidene-3-*O*-*tert*-butyldimethylsilyl-1,2-dideoxy-1-pyridinylsulfonyl-β-D-glucopyranose (**6**), and the aldehyde, *p*-methoxyphenyl 2,3-di-*O*-benzyl-4-deoxy-4-*C*-formyl-6-*O*-*p*-methoxybenzyl-β-D-glucopyranoside (**14**).

Keywords: *C*-Glycosyl compounds; C-Glycosides; C-Disaccharide; Hyaluronic acid mimetic; Samarium diiodide

1. Introduction

Hyaluronic acid (hyaluronan, HA, Fig. 1) is a polysaccharide of high molecular weight ($M_r > 10^6$) that is composed of a repeating disaccharide unit in which D-glucuronic acid is linked to the 3-position of 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine), that is, $[\rightarrow 3)$-β-D-GlcNAc-$(1\rightarrow 4)$-β-D-GlcA-$(1\rightarrow)]_n$. HA, which is synthesized in the plasma membrane and is associated with the complement of glycosaminoglycans (GAGs) located in the extracellular matrix, has a variety of functions in the human body. For example, it serves as the gelling agent of the vitreous body of the eye, is a component in the lubricants associated with the synovial fluid in joints, and is found in significant quantities in the placenta.[1,2] A process that has come to the forefront in recent years concerns the role that HA plays in the metastasis of cancer: the binding of a migrating cancer cell's CD44 receptor to HA performs a critical role in the metastasis of certain cancers, especially the migration of melanoma cells to the lung.[3] Several lines of evidence further implicate that this CD44–HA interaction facilitates cell movement in cancer cells during metastasis.[4–6]

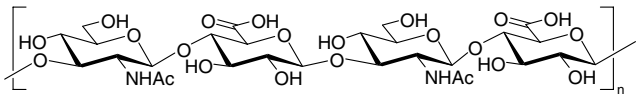

Figure 1. Hyaluronic acid (hyaluronan, HA).

As a part of an ongoing project, the goal was to synthesize a 'C-disaccharide' that would be a mimetic for the repeating unit of HA and would be totally resistant, due to the interresidue C–C–C linkages, to enzymes that degrade the natural polymer. Further objectives are to study its conformation and incorporate it into a synthetic oligosaccharide in such a way that the oligomer would be resistant to enzymes that degrade HA. Herein is presented a total synthesis of the target C-disaccharide as its *p*-methoxyphenyl glycoside.

2. Results and discussion

2.1. Synthetic approaches

Approaches to C-linked disaccharides (*C*-glycosylic compounds, often referred to as 'C-glycosides') are varied;[7,8] however, the success in any *C*-glycosylic coupling depends on the peculiar reactivities of the sugar units (i.e., whether primary or secondary carbon atoms are

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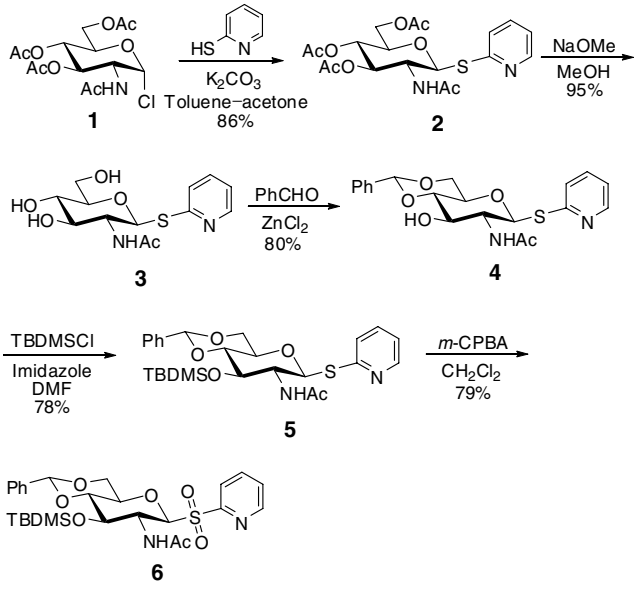
targeted in the glycosyl acceptor), as well as the stabilities of the protecting groups involved and their influence on the reactivity of both the glycosyl donor and acceptor. For our purposes, several processes were attempted in this laboratory,[9–11] among them the Henry coupling advocated by Martin and Lei,[12,13] the olefin metathesis method of Postema and co-workers,[14,15] as well as the dianion approach advocated by Kessler and co-workers.[16,17] Of these, only the latter method, which had been developed for simple *C*-glycosyl–alkyl conjugates, gave good results with our specific compounds that have multiple functionalities present; however, this rather harsh organometallic reaction limited the type of OH protection that could be employed, which limited future possibilities in construction of more complex *C*-glycosylic compounds. Another approach that involves the use of samarium diiodide-mediated coupling of a glycosyl sulfone (donor) with a *C*-formyl sugar (an aldehyde, the acceptor), as developed by Beau and co-workers for glucosamine derivatives[18–22] and by Linhardt and co-workers[23,24] for the synthesis of sialic acid mimetics, was carried out and gave the most promising results. Using this SmI_2 strategy, the synthesis, which makes use of the glycosyl donor **6** and the acceptor **14**, was carried out as described in the following sections.

2.2. Synthesis of protected sulfone 6

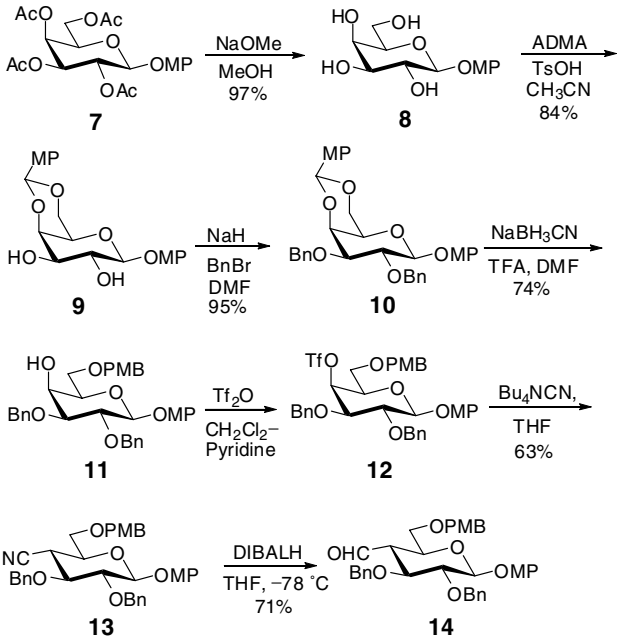
The synthesis of sulfone **6** was carried out as shown in Scheme 1. Thus, the reaction of glycosyl chloride **1** with K_2CO_3 and 2-mercaptopyridine in dry acetone at 50 °C gave the desired pyridinyl thioglycoside **2**.[25] In order to manipulate the protective groups, **2** was treated with NaOMe in 1:5 CH_2Cl_2–MeOH to afford the free-hydroxy compound **3** that was directly reacted with benzaldehyde and $ZnCl_2$ at room temperature for 16 h to give the 4,6-O-benzylidenated **4**.[26,27] Treatment of **4** with *tert*-butylchlorodimethylsilane (TBDMSCl) in the presence of imidazole in DMF at room temperature overnight[28] gave compound **5**, which was readily converted to the corresponding protected sulfone **6** in 79% yield via treatment with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 at 0 °C.[19] The β configuration for **6** was clearly indicated by the doublet for H-1 at δ 5.81 ($J_{1,2} = 10.3$ Hz); furthermore, there was no resonance indicative of any α anomer.



Scheme 1. Synthesis of the *C*-glycosyl donor, protected sulfone **6**.

2.3. Synthesis of protected aldehyde 14

The synthesis of aldehyde **14** proceeded from known compound **7**[29] as shown in Scheme 2. Deacetylation of **7** with NaOMe in 1:5 CH_2Cl_2 and MeOH gave the corresponding tetraol **8** in nearly quantitative yield. Regioselective bis-protection of the 4-OH and 6-OH positions with a *p*-methoxybenzylidene group was accomplished via treatment of **8** with anisaldehyde dimethyl acetal (ADMA) in the presence of a catalytic amount of *p*-TsOH in dry CH_3CN to afford diol **9** as a precipitate in 84% yield.[30] The resulting diol **9** was then treated with NaH at 0 °C for 10 min, followed by addition of benzyl bromide in DMF, to give O-dibenzylated **10** in 95% yield. Regioselective reductive cleavage of the benzylidene ring of compound **10** was achieved via treatment with $NaBH_3CN$ and CF_3CO_2H in the presence of 4 Å MS in DMF at room temperature for 10 h to render 4-OH isomer **11** in 74% yield as the major product, along with the 6-OH isomer as a byproduct (21%, data not provided).[31] Treatment of compound **11** with



Scheme 2. Synthesis of *C*-glycosyl acceptor, aldehyde **14**.