Life science

Harnessing free sulfate groups in glycosylation reactions

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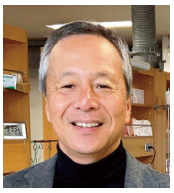

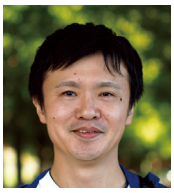

Abstract

In this study, we developed a novel glycosylation reaction in the presence of free sulfate groups. Because sulfate groups are inherently unstable functional groups that can undergo side reactions such as elimination, we first investigated the properties of unprotected sulfate groups in detail. As a result, we found that free sulfate groups are stabilized when Na^+ or Li^+ cations are used as counterions. We then activated the sulfate-containing sugar donor under mild conditions using a gold catalyst, successfully giving the desired glycosylation products in good yields. Furthermore, even in the presence of a free sulfate group, the acyl protecting group introduced at the C-2 position enabled neighboring-group participation, thereby ensuring the desired β-selectivity. Using this newly developed glycosylation method, we successfully synthesized the chondroitin sulfate (CS) tetrasaccharides.

Background & Results

Chemical synthesis of sulfated oligosaccharides typically requires protection of sulfate groups during glycosylation or post-sulfation after assembly of the oligosaccharide backbone. However, the reactivity and stability of free sulfate groups under glycosylation conditions have remained largely unexplored.

In this study, we systematically investigated glycosyl donors bearing unprotected sulfate groups. Activation of 6-sulfated GalNAc donors (**1**,**2**) having either 2-O-acetyl or 2-NHTroc groups and an *o*-hexynylbenzoate leaving group at the anomeric position afforded β-glycosides (**3**,**4**) in good yields. These results demonstrate that glycosylation can proceed efficiently in the presence of a free sulfate group, while retaining neighboring-group participation (intermediate **B**) by the 2-NHTroc and 2-O-acetyl groups. Ab initio calculations supported formation of an acyloxonium ion intermediate **B** through 2-O-acyl participation. Furthermore, investigation of the effect of counterions revealed that sodium and lithium sulfate salts afforded the best reactivities and product yields.

Finally, glycosylation using disaccharide donor **10** and acceptor **11** containing free sulfate group, that were synthesized from isolated disaccharide **7**, successfully yielded sulfated chondroitin sulfate (CS) tetrasaccharides, highlighting the utility of this strategy for the direct synthesis of sulfated glycans.

Significance of the research and Future perspective

Chondroitin sulfate (CS) is an important bioactive molecule involved in cellular differentiation, neuronal axon growth, and other biological processes. CS consists of repeating disaccharide unit (N-acetylgalactosamine (GalNAc) and glucuronic acid (GlcA)). The biological functions change depending on the sulfation pattern of the hydroxy groups. Conventional chemical synthesis requires the introduction of sulfate groups at the final stages or the use of protecting groups for sulfate groups, leading to an increased number of steps and limitation of synthetic strategy. In contrast, our approach enables the flexible synthesis of CS oligosaccharides, and our method can advance the elucidation of CS functions using synthetic homogeneous glycans.

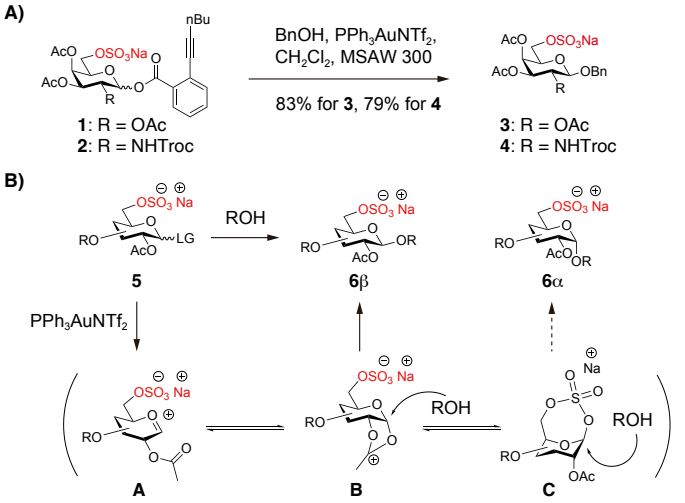

Figure 1 Novel glycosylation reaction using a glycosyl donor having free sulfate

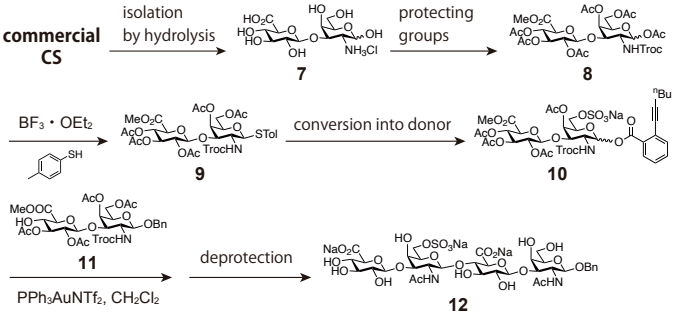

Figure 2 Semisynthesis of chondroitin sulfate

Patent

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