Principal Investigator: Go Hirai
Grant Title: Development of novel mechanism-based inhibitors for glycohydrolases

Abstract

Our laboratory is focusing on the development of *pseudo*-glycans, which we define as glycan or glycoconjugate analogues with very small structural modifications that enhance the original function of the parent molecule in cellulo/in vivo or result in the acquisition of a new function. One of our important achievements is the development of metabolically-stable analogues of glycolipid ganglioside GM3[1]. We are now trying to develop glycohydrolase-resistant analogues of other glycans and glycoconjugates, using our own direct C-glycosylation methodologies[2-4].

In this project, we have been focusing on the development of different type of *pseudo*-glycans with exomethylene functionality next to anomeric position[5]. To date, we have identified biological potentials for this type of *pseudo*-glycans and have already completed patent applications. However, the development of a method for synthesizing *pseudo*-glycans with β-glycosidic linkages has remained unexplored. In this study, we first investigated the construction of a stereoselective β-glycosidic linkage based on hydrogen bond-mediated aglycon transfer reaction, developed by Prof. Demchenko and co-workers, and found that β-selectivity was somewhat achieved by using primary alcohols as nucleophiles. However, the selectivity was decreased in the case of bulky nucleophiles, such as secondary alcohols.

We then envisioned Pd-catalyzed Tsuji-Trost-type glycosylation and realized the "ligand-controlled" synthesis of *pseudo*-glycans with both α- and β-glycosidic linkages in high stereoselective manners. Based on this strategy, we have completed the synthesis of our target compounds including *pseudo*-glucosylceramides. Preliminary investigation suggested their unique biological activities [6].

References

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