Principal Investigator: Hiromune Ando
Grant Title: Innovation of the glycosidation reaction of sialic acid

Abstract

1. Research objective: α-Selective glycosidation of sialic acid has remained a grand challenge in carbohydrate chemistry. To surmount the sensitivity to the structure of reaction substrates and reaction conditions of the precedent methods, we envisioned a novel substrate-controlled system for producing α-sialosides, in which macrobicyclic sialic acid derivatives with α-configuration were used as the synthetic equivalent of bridgehead oxocarbenium ion of sialic acid that would restrict the attack of the nucleophile on the α-face. The preliminary study revealed that a sialic acid donor with a bicyclo[12.2.2] system provided the highest yield of the α-glycoside with complete stereoselectivity. Based on the proof-of-concept, this project aimed to establish a comprehensive method for making α-sialyl molecules.

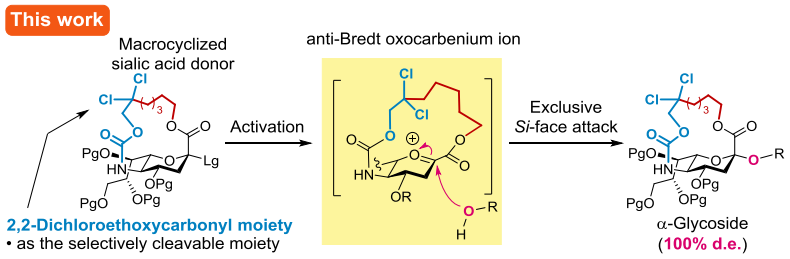
2. Results

2.1. Substrate scope: Examination of the glycosidation reactions of bicylclic sialic acid donors bearing a phenylsulfenyl moiety and a dibenzylphosphate moiety as a leaving group revealed broad substrate scope, including primary to tertiary hydroxyl groups linked to sugar and nonsugar backbones. Primary and secondary hydroxyl groups in an oligosaccharide acceptor were simultaneously sialylated in a stereo- and regioselective manner to produce disialylated glycan in high yield. Due to its oxidant free condition, a phosphate sialyl donor ensured to glycosylate unsaturated substrates. Furthermore, phosphate donor was reacted with carbon nucleophiles such as metallyltrimethylsilane and silylenol to give the corresponding *C*-glycosides in high yields.

2.2. Selective cleavage of the tethering and subsequent modification of 5-NH_2 group: Due to the 2,2-dichloroethoxycarbonyl moiety, the tethering at the C-5 amino group was selectively cleaved upon treatment of zinc to give 5-NH_2 intermediate, which was transformed to sialic acid congeners by acyl modification, giving N-Ac, N-Gc and N-FucosylGc derivatives.

2.3. Synthesis of oligomeric sialic acids: It was found that the 8-OH of macrobicyclized sialic acid was exposed outward and showed ameliorated reactivity compared to that of normal sialic acid. This finding allowed for the design of the synthesis of α(2,8)-linked oligomeric sialic acid, which is most challenging in carbohydrate synthesis. A bicyclic sialic acid donor with tentative protection at the 8-OH underwent the cycle of glycosidation and deprotection at 8-OH, producing a petameric sialic acid derivative. Full deprotection has delivered unprotected pentasialoside.

3. Conclusion: A substituent of the sialic acid, the C-1 carboxyl group, which is generally detrimental to the glycosidation, was instead harnessed as the key to solving the long-standing issue of α-sialidation. These results also represent the achievement of a general, substrate-controlled stereoselective glycosidation. The prominent features of our method, including complete stereoselectivity, high glycosidation yield, broad substrate scope and high applicability toward sialic acid congeners, could revolutionize the synthesis of sialoglycans.



4. Publication

N. Komura *et al. Science*, **2019**, *364*, 677-680.