Synthesis of acetic acid bacteria *Acetobacter pasteurianus* lipid A

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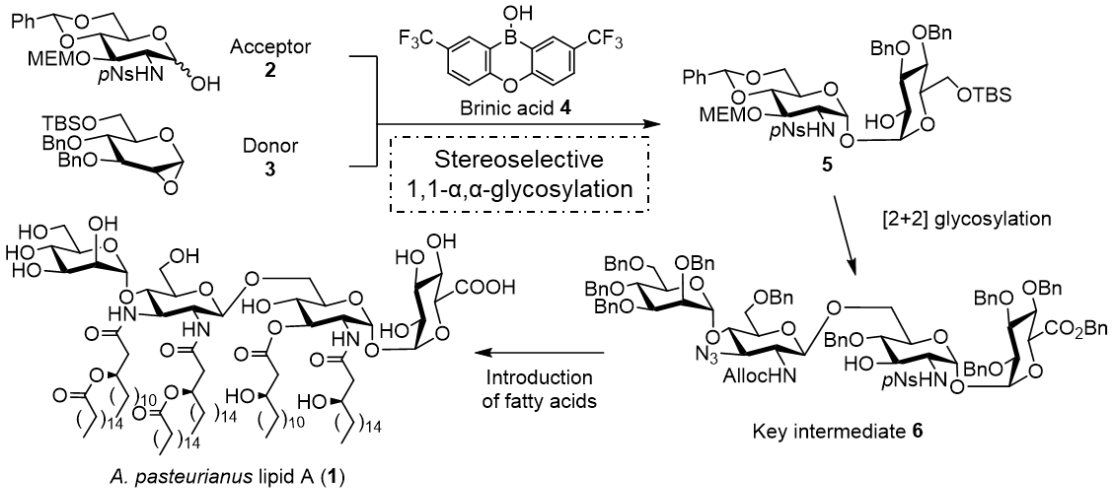
Lipopolysaccharide (LPS), one of the cell surface components of Gram-negative bacteria, activates innate immunity. LPS and its active entity lipid A are candidates for vaccine adjuvants that enhance the effectiveness of vaccine. Many bacterial LPSs such as canonical *Escherichia coli* LPS have strong immunostimulatory function but highly inflammatory effect and lethal toxicity. Therefore, it is essential to control the toxicity in order to apply LPS and lipid A to adjuvants.

In this study, we focused on an acetic acid bacteria *Acetobacter pasteurianus* lipid A (**1**)[1], which is expected to be safe through food experience, as a low-toxicity adjuvant (Scheme 1). *A. pasteurianus* lipid A (**1**) contains a unique tetrasaccharide backbone that is unprecedented in synthesis. Here, we investigated the efficient construction of 1,1-α,α-glycosidic linkage of **5** and found that 1,2-*cis*-glycosylation between **2** and **3** catalyzed by borinic acid **4**[2] afforded **5** in high yield and stereoselectivity. Next, [2+2] glycosylation was used to synthesize the key intermediate **6** with orthogonal protecting group pattern. After introduction of various fatty acids into appropriate positions of **6**, all protecting groups were removed by catalytic hydrogenolysis to achieve the first chemical synthesis of *A. pasteurianus* lipid A (**1**). Its biological activity is now under investigation.



Scheme 1. Synthesis of *A. pasteurianus* lipid A (**1**)

1) M. Hashimoto, K. Fukase, Y. Fujimoto, et al., *J. Bio. Chem.*, **2016**, *291*, 21184–21194. 2) Y. Takemoto, et al., *Angew. Chem. Int. Ed.* **2020**, *59*, 14054–14059