Synthesis and immune function of acetic acid bacteria Acetobacter pasteurianus lipid A

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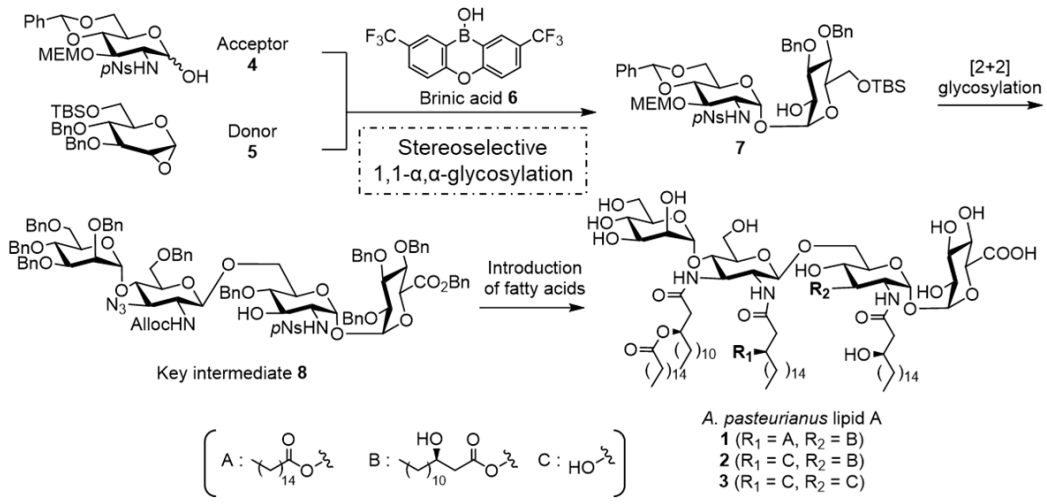
Lipopolysaccharide (LPS), one of the cell surface components of Gram-negative bacteria, activates innate immunity. LPS and its active entity lipid A have potential as adjuvants that enhance the vaccine efficacy. However, canonical Escherichia coli LPS has highly inflammatory effect and exhibits lethal toxicity, necessitating the need to control its toxicity for application in adjuvants.

In this study, we focused on an acetic acid bacteria Acetobacter pasteurianus lipid A 1, which is expected to be safe due to its use in food, as a low-toxicity adjuvant. A. pasteurianus lipid A contains three types of lipid A 1-3 (Scheme 1) with different fatty acid patterns, which possess a unique tetrasaccharide backbone for which chemical synthesis has not yet been achieved. We investigated the efficient construction of 1,1-α,α-glycosidic linkage of 7 and found that 1,2-cis-glycosylation between 4 and 5, catalyzed by borinic acid 6,2 afforded 7 in high yield and stereoselectivity. We used [2+2] glycosylation to synthesize the key intermediate 8 with an orthogonal protecting group pattern. After introduction of various fatty acids into appropriate positions of 8, all protecting groups were removed by catalytic hydrogenolysis to achieve the first chemical syntheses of 1-3. We evaluated their immunostimulatory activities and found that 1 is most active among 1-3, identifying 1 as the active entity of A. pasteurianus LPS. The adjuvant activity of 1 is currently under investigation.



Scheme 1. Syntheses of A. pasteurianus lipid A 1-3

Bibliographic references:

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2) Y. Takemoto, et al. (2020), Angew. Chem. Int. Ed. (59) 14054–14059.