Synthetic study of lipid conjugates containing sugar-modified fatty acids as ligands of the innate immune receptor Mincle

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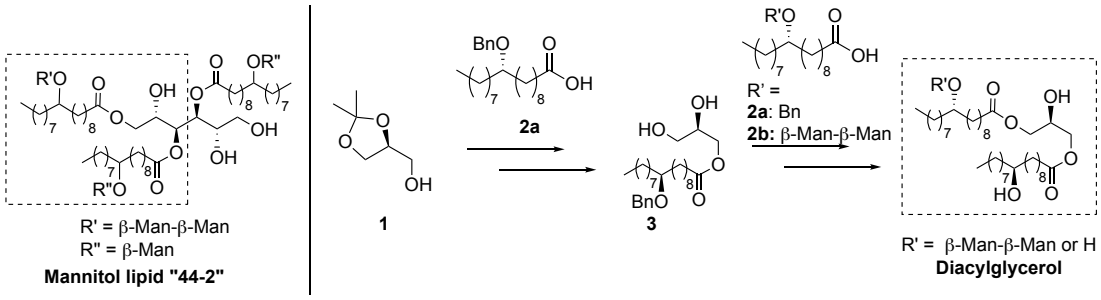
Mincle, a C-type lectin receptor, recognizes various kinds of lipid conjugates, leading to the activation of the innate immune system. The ligand molecules recognized by Mincle include glycero- or mannitol lipids, along with the better known trehalose-containing glycolipids.[1,2] Recently, a mannitol lipid conjugate "44-2", having sugar-modified fatty acids, was discovered as a Mincle ligand showing potent Mincle-mediated signaling activity. However, the molecular basis of the signaling activity is still unclear. In this study, in order to investigate the detailed structure-activity relationships of Mincle ligands, especially ones having unique lipid moieties, we developed a synthetic method for sugar-modified fatty acids containing 1,3-diacylglycerol and related compounds.

As shown in the scheme, for the synthesis of the desired compounds we established a synthetic method to modify the lipid with glycans and to introduce unique modified fatty acids to 1,3-diacylgylcerols. First, the benzyl protected fatty acid **2a** and β-mannosylated fatty acid **2b** were prepared from chiral hydroxy fatty acids, obtained by optical resolution of racemic methyl 10-hydroxyoctadecanoate. The key intermediate 1-acylglycerol **3** was prepared by esterification of the appropriately protected glycerol **1** and subsequent cleavage of acetal protection. Selective esterification of **3** with fatty acid **2a** or **b** and hydrogenation gave the respective 1,3-diacylglycerols. The established synthetic strategy will be applied for divergent synthesis of 1,3-diacylglycerols containing various lipids.



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