Synthesis and Biological Evaluation of C-Linked α-Galactosylceramide Analogs

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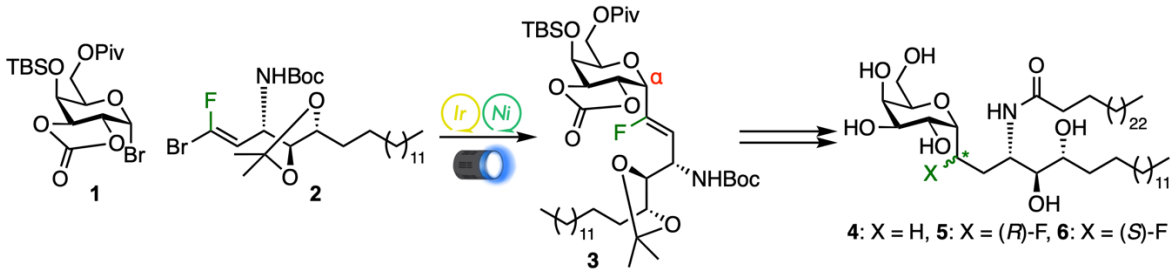
α-Galactosylceramide (α-GalCer) is a potent immunostimulatory glycolipid with therapeutic potential for cancer and infectious diseases.[1] According to previous SAR studies,[2] CH_2-linked analog of α-GalCer stimulates an enhanced Th1-type response. Here, we developed new synthetic methods for *C*-glycoside analogs of α-GalCer, including CH_2-, (*S*)-CHF-, and (*R*)-CHF-linked analogs that would adopt different conformations around glycoside bonds due to stereoelectronic effect of fluorine atom, and evaluated their biological activities.

In our previous work, we developed a direct cross-coupling method for glycosyl xanthate and terminal olefin using atom-transfer radical addition.[3] This method resulted in the formation of *C*-glycosides in an α-selective fashion. In particular, coupling a galactose-type donor with a sphingosine-type acceptor led to the production of α-*CH_2*-galactosylsphingosine, which was then further transformed into a *CH_2*-linked analog of α-GalCer.[4] Unfortunately, the method could not produce *CHF*-glycosides analogs due to the unreactive nature of the fluoroalkene.

This work synthesized CH_2- and CHF-glycoside analogs using a direct cross-coupling reaction of glycosyl bromide donor **1** and BrF-olefin acceptor **2** in the presence of Ir-photocatalyst and Ni-catalyst under blue LED irradiation, affording the fluoroalkene **3** in an α-selective manner. The chemo- and stereo-selective hydrogenation of **3** followed by deprotection and acylation successfully afforded CH_2-, (*S*)-CHF-, and (*R*)-CHF analogs of α-GalCer (**4**, **5**, **6**). In this presentation, we present the detail of the synthetic method and biological activity of the synthesized α-GalCer analog.



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