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Synthesis of Glycopharmaceuticals for the Treatment of Microbial Sepsis

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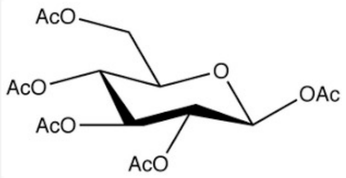
Carbohydrates

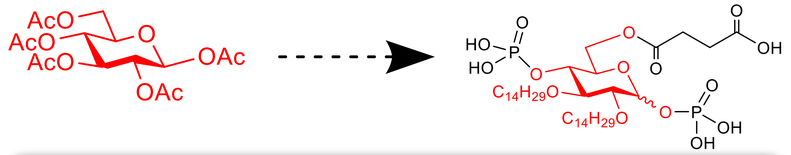
Carbohydrates use sugar building blocks to create large, multilinked structures. Although having many uses such as cell metabolism, there are many potential pharmaceutical uses for these chemicals. Current studies include carbohydrate functionalized nanoparticles for drug discovery. In addition, polyethylene glycols are often attached to bioactive molecules to improve pharmacokinetic profiles (PEGylation). There is no question for the importance of carbohydrates in the pharmaceutical discipline, and this project uses organic reactions already known to create a novel molecule.



Gram-Negative Bacteria

One way that bacteria is classified is from the Gram test, which the bacteria are stained with certain dyes to determine cell wall make up. Gram-negative bacteria do not take up this stain, and have a specific feature of a molecule called Lipopolysaccharides (LPS). This molecule makes up the outer leaflet of the outer membrane of most of these bacteria. Also known as an endotoxin, when these bacteria are broken down in an infection, they release these LPS molecules into the host's body. For humans, this triggers the CD14 receptor, causing an overreaction by the host's own immune system in sepsis. The overreaction includes a release of proinflammatory cytokines, which eventually can lead to damage and death of host cells and tissues.

Results

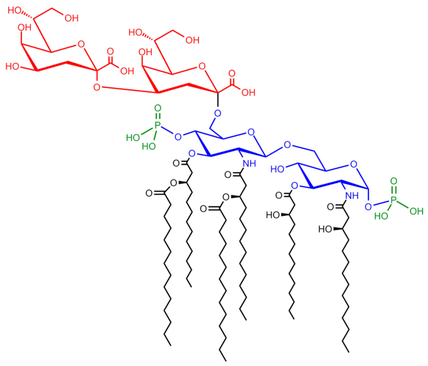


This project is an ongoing effort in an over 12 step synthesis, starting from glucose pentaacetate and ending with the target chemical. For the novel compound, there is a succinoyl at the 6 carbon, along with C14 chains at the 2 and 3 carbons. Lastly, there are phosphates at the anomeric and 4 carbon. Being an ongoing effort the novel target chemical has not been synthesized yet, and the reactions is currently on step 9. Results and reactions are below:

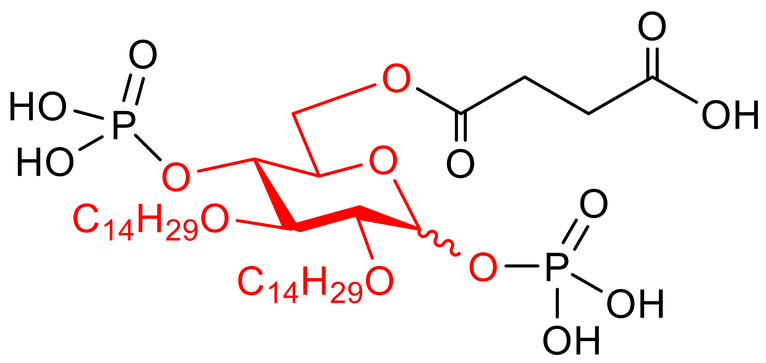
Reaction	Description of Reaction	Percent Yield
1	SEt Introduction	90
2	Deacetylation	98
3	Benzylidine Introduction	85
4	C14 Introduction	90
5	Selective Benzylidine Opening	80
6	Succinoyl Introduction	74
7	Benzyl Introduction	60
8	SEt Removal	85
8	pMB Removal	82

Blocking the CD14 Receptor

Using simulations of the receptors, Potential molecules are determined that may have binding potential to the CD14 receptor. The potential molecules are ranked based on binding affinity, and a multistep synthesis is determined to create the target molecule. By blocking this receptor, the LPS molecule is not able to bind to it, leading to a lessened immune response to the release of these molecules

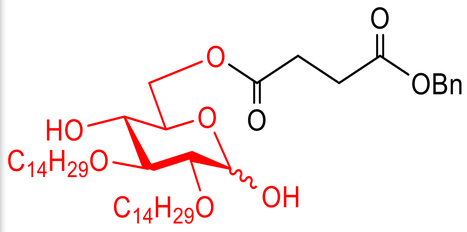


Molecule of Interest



Current Molecule

The current molecule has most of the substituents that are in the target molecule. The C14 chains are attached to the 2 and 3 carbons, as well as the succinoyl on 6 carbon. The next steps are to phosphorylate the OH groups on the 1 and 4 carbon, and then remove the benzene on the succinoyl group



Conclusions

Because the synthesis has been successful until step 9, this molecule shows promise in the realm of being created. When this novel glycopharmaceutical is created, it will be tested on how well it blocks binging to the CD14 receptor. Further reactions will be conducted to synthesize the molecule of interest, and if it is not promising when tested for bioactivity, a different molecule, but similar molecule can be synthesized as given by simulation.

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