Exploring Regioselective 5*N*-acylation of Neuraminic acid

Simon Hans Lilje

Degree Project in Subject, 2022
Department of Chemistry
Lund University
Sweden

MSc, 15 hp

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28.10.2022
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Supervisor:
Joachim Björklund
M.Sc

Examiner:
Ulf Ellervik
Prof. Dr.

Lund University
Department of Chemistry
Centre for Analysis and Synthesis
P.O. Box 124
SE-221 00 Lund, Sweden

Synthesis of cell-surface sugars

Sugars are in addition to proteins and nucleic acids one of the main components of life. The most prominent example, related to this work is the immune system. Most of the key molecules involved in the innate and adaptive immune response are glycosylated,[1] meaning their specific function mainly relies on the different sugar chains, attached to proteins and lipids. Sialic acid is used in higher organisms during intercellular communication as a signalling molecule on cell surfaces.

By using molecular mimicry, pathogens disguise themselves from the host cell's immune response by mimicking the host cell surface. There are four known different transporter families, capable of binding sialic acid and transporting it into cells. By small chemical variations in the molecular structure of sialic acid, it is possible to clog these transporters, inhibiting the uptake of sialic acid and thereby supporting the immune system by preventing the pathogen from maintaining its disguise. To find promising clogs, a huge number of different modifications of sialic acid are synthesized and tested for their clogging properties.

The current problem is to incorporate small chemical variations into the sialic acid molecule. Due to its higher complexity compared to other sugars, which are defined by many functional groups with nearly the same reactivity, lots of preparatory steps are needed before each position can selectively be modified. Recently, a new method was published to directly modify one of these reactive positions in one step without interference, saving preliminary steps. This represents a huge reduction in time and financial resources.

My internship aims to test the new method and extend the currently existing library of modifications for this special position. The new method was tested, and three new compounds were synthesized but the handling isn't as straightforward as promised. In future, the reaction conditions and the processing must be optimized to avoid side reactions and to isolate the expected product in a high yield, respectively.

Abstract

In this project, a regioselective method to deprotect and acylate the amide on C5 of sialic acid is explored. Sialic acid is one of the most complex monosaccharides and is an important ligand in many higher organisms in intercellular cell communication. The most prominent example is related to the immune system. Sialic acids are attached as the terminal carbohydrate on cell surface glycans, which is one of the unique patterns, used to distinguish between enemy and friend. Most pathogens need to take up sialic acid from their host, either to use it as an additional energy source or to incorporate it in their cell surface glycans to mimic the host cells. This mechanism leading to disguise is called molecular mimicry. The long-term aim is to find sialic acid derivatives to clog the transporters of the pathogens, resulting in a better immune response. Synthesising derivatives of sialic acid isn't trivial due to its carboxylic acid function next to the anomeric hydroxyl group, four additional hydroxyl groups and an amide. This multitude of functional groups requires elaborate protection group strategies, which make it possible to address functional groups regioselectively. The simplest protecting strategy for sialic acid is the esterification of the carboxylic acid and per acetylation of all the hydroxyl groups. The problem was to remove just one of these acetyl groups. The new method, which is explored in this project enables the removal of the acetamide from C5 of sialic acid, enabling an easy and fast amidation of C5, saving four steps compared to the current synthetic pathway. However, side reactions made the synthesis of new compounds more difficult than expected, so just a few new compounds were observed in NMR and three were isolated. All in all, the reaction conditions, especially for the amidation and the processing of the reactions have to be optimized before simple synthesis is possible via this route.

Keywords: acylation, amide, antibacterial drugs, regioselective deprotection, sialic acid