Abstract

Title of the Master thesis: *Synthesis of ceramides derived from 6-hydroxysphingosine*

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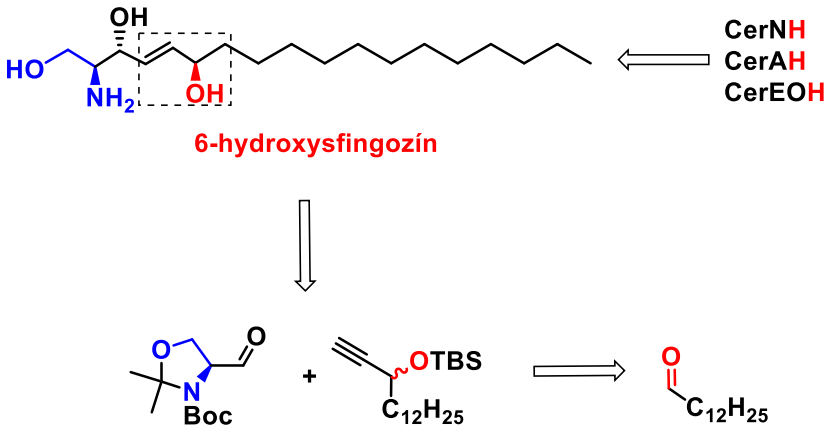
Ceramides (Cer), belong to the group of sphingolipids naturally found in each cell. One of their principal functions is cell signaling. We can find Cer in the uppermost layer of epidermis (stratum corneum), where the concentrations of these lipids are highest in the whole human body. Cer form an intercellular multi-lamellar lipid matrix. This lipid mass is composed of cholesterol and free fatty acids as well. The major function of stratum corneum is to protect the body from the excesive transepidermal water loss, provide internal homeostasis and create a protective barrier against harmful substances from external environment.

Cer are amides of long aminoalcohols with a fatty acid attached to their primary amino group. 6-hydroxysphingosine (H) is specific for human epidermis, but its function and biosynthesis in skin is still not completly understood. Some studies showed lower concentrations of 6-hydroxysphingosine-based Cer in skin of patients suffering from atopic dermatitis.

The aim of this project was to optimize individual steps of H total synthesis to reach higher yields and to enable the synthesis in higher scale.

The retrosynthetic analysis of H-derived Cer shown in Scheme 1 provides H and the corresponding fatty acid in the first step. Due to the specific stereochemistry of the polar head of sphingoid bases, this part is biosynthetically introduced into the molecule by *L*-serine. Synthetically, this fragment can be found in the so-called Garner aldehyde ((*S*)-GA), which can react with a suitable nucleophile.

The synthesis of H was therefore based on the alkynylation of *(S)*-GA with protected *(R)*-pendadec-1-yn-3-ol followed by chromatographic separation of the individual diastereomers formed. The next key step was the selective reduction of the triple bond to a *trans*-double bond (which was one of the partial goals of this work) and deprotection gave the final 6-hydroxysphingosine.



Scheme 1 Retrosynthesis of physiological 6-hydroxysphingosine and H-Cer.

Physiological H was prepared in 7 steps, 5 of which were the content of this work with a total yield of 21%. The sphingoid base formed in this way was used for the preparation of CerNH, CerAH, CerEOH in the next step of this project.