Abstract

Title of the Master thesis: *Synthesis and evaluation of human 6-hydroxyceramides*

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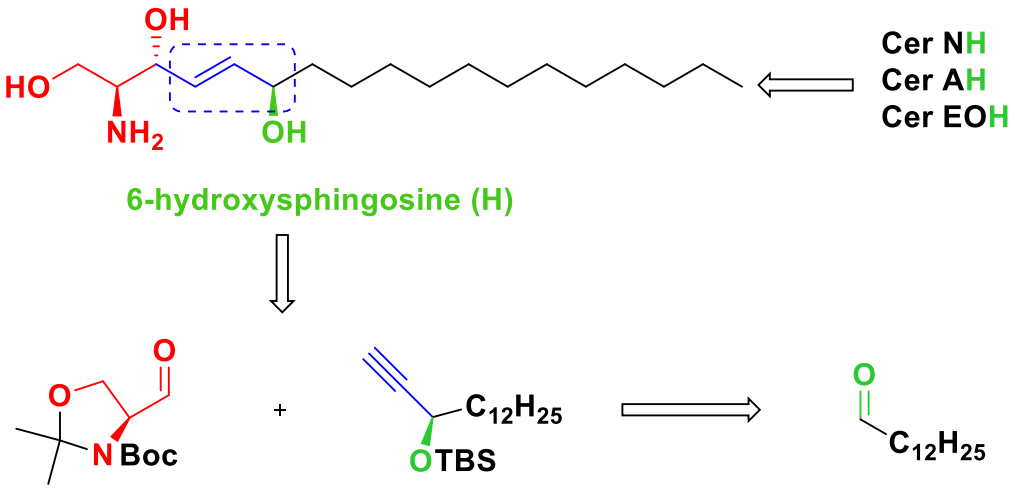
Ceramides (Cer), the members of sphingolipid family, occur in all human cells and play an important role in cell signaling. In high concentrations, Cer can also be found in the uppermost layer of epidermis called *stratum corneum*, along with free fatty acids and cholesterol (in equimolar ratio), where they form the intercellular multi-lamellar lipid matrix. The key function of *stratum corneum* is to ensure a permeability barrier, thus, to provide water and electrolyte homeostasis, and to prevent entry of harmful substances into the organism.

Cer are composed of a sphingoid base and an acyl part derived from a long-chain fatty acid. Cer based on 6-hydroxysphingosine (**H**) are amongst the most unusual sphingolipids. In contrast to sphingosine-based Cer, 6-hydroxysphingosine-based Cer (**H-Cer**) are unique for the epidermis and, in addition, H-Cer are not typical for all mammals. Moreover, the function and biosynthesis of H-Cer in the skin is still not completely understood. Several dermatological studies showed that lower concentrations of H-Cer in skin accompany several skin diseases, such as atopic dermatitis. The major limitation of understanding the importance and uniqueness of H-Cer is their commercial unavailability. Therefore, the aim of this work was to explore a new synthetic route towards H as a precursor of all H-Cer subclasses.



Scheme 1. *Structure and retrosynthesis of physiological 6-hydroxysphingosine, i.e., (2S,3R,4E,6R)-2-aminooctadec-4-ene-1,3,6-triol and H-Cer.*

The total synthesis of (**H**) was based on the reaction of commercially available tridecanal with trimethylsilyl acetylene. The strategy for the synthesis of H involved an alkynylation of (*S*)-Garner's aldehyde (a protected *L*-serinal) with protected (*R*)-pentadec-1-yn-3-ol followed by a selective two-step reduction of the triple bond to a *trans*-double bond. In this step, a mild and selective $[Cp^*Ru(CH_3CN)_3]PF_6$-catalyzed Trost's hydrosilylation followed by protodesilylation was used.

In conclusion, physiological H has been prepared in seven reaction steps with overall yield 40 %. This base was then used for the preparation of Cer NH, Cer AH and Cer EOH.

Additionally, the phase behaviour and biophysical properties of Cer NH have been studied using model lipid membranes. In these experiments, we discovered a specific CerNH chain order, different phase transitions of CH_2/CD_2 chains, tight orthorhombic lateral packing and decreased miscibility of Cer NH with other skin lipids.