Jorin Hoogenboom

Supervisor(s)	Dr. Tom Wennekes, Prof. Dr. Han Zuilhof
Project	**The total synthesis of a novel activity-based probe for sialidases**
Fields of interest	Synthetic chemistry, and chemical biology
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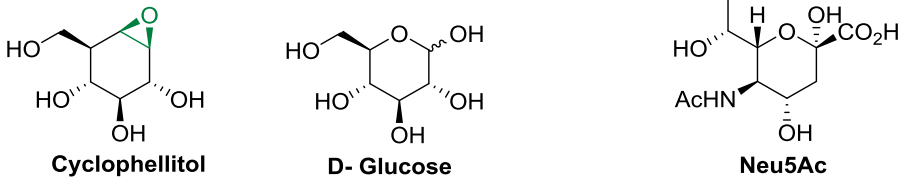
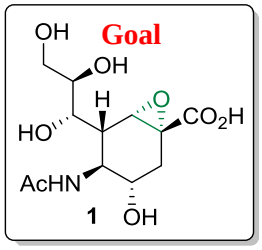
Introduction

(+)-Cyclophellitol is a natural inhibitor of β-glucosidases. This enzyme inhibitor is a carbocyclic analogue of glucose and is able to irreversibly bind in the active site of β-glucosidases with very high selectivity. Sialidases are a class of enzymes that are involved in the lifecycle of sialic acids (e.g. **Neu5Ac**), which are a specific class of sugars that are mainly found in animals tissue and critical in communication between cells. However, in contrast to glucosidases, sialidases have been rarely studied.

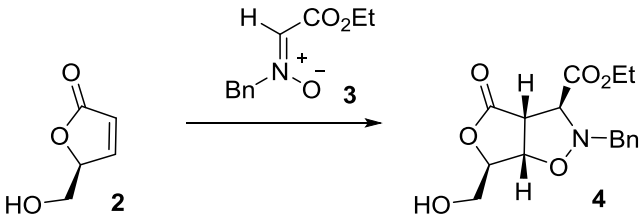
Inspiration

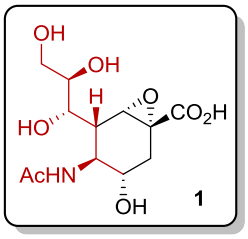




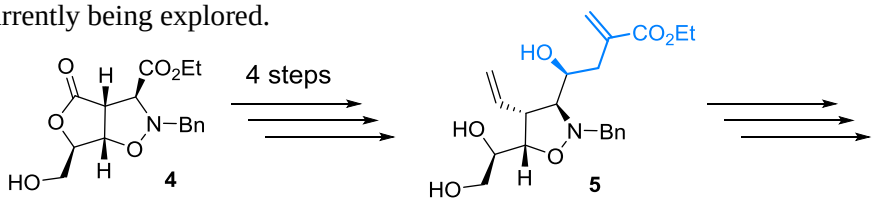
Goal

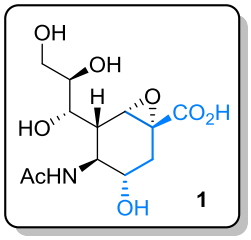
We aim to synthesize the carbocyclic analogue **1** of Neu5Ac with a reactive epoxide in the carbocycle. Sialidases are highly selective towards sialic acids such as Neu5Ac and we propose that incorporating an epoxide in the carbocycle ring would enable irreversible binding of sialidases to carbocycle **1**. This process would then allow the study of sialidases in vitro and in vivo. A major part of the backbone of the desired carbocycle can be obtained in a single step through a 1,3 dipolar cycloaddition reaction between an alkene **2** and a nitrone **3** as shown below.





It was found that this reaction allows the introduction of as much as 3 additional chiral centres without the aid of any catalyst. Several routes towards intermediate **5** and finally product **1** have been proposed and is currently being explored.





Acknowledgement

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