Acetogenins: Chemoenzymatic Synthesis And Molecular Probing Of Respiratory NADH Dehydrogenases

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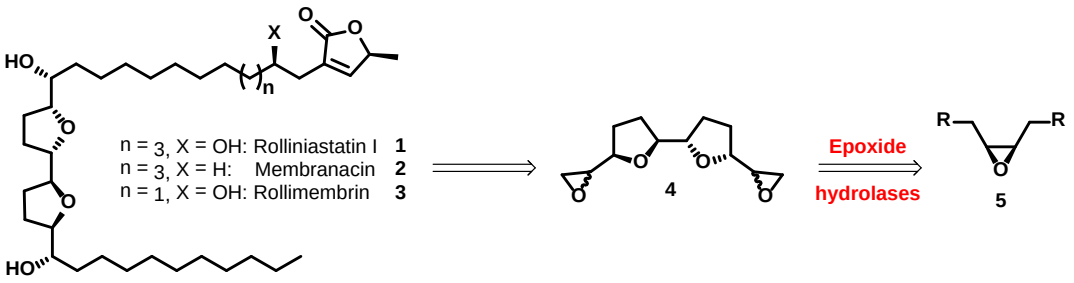
Complex I (NADH dehydrogenase) plays a central role in cellular energetics and is a major source of reactive oxygen species (ROS).[1] It appears that tumour cells are closer to excessive ROS generation than healthy cells due to a more negative redox potential of the NAD(H) couple.[2] Therefore, Complex I is an interesting target for differential drug design.[3]

The most potent among the many structurally diverse inhibitors of Complex I are the annonaceous acetogenins, a large class of polyketide natural products isolated from the *Annonaceae* family of flowering plants.[4] The typical structure of these compounds comprises of a (*S*)-5-methylbutenolide ring substituted at the 3-position with a long linear aliphatic chain incorporating often two tetrahydrofuran (THF) fragments (*e.g.* compounds **1**, **2** and **3**).



We envision that the bis-THF-bis-epoxides **4** can be synthesized stereoselectively from *meso*-epoxides **5** by biocatalytic hydrolysis, using a broad range of epoxide hydrolases from the collection hosted at the University of Graz.[5] The multidisciplinarity of this project will be underscored by highlighting both the synthetic organic chemistry and chemical biology.

1 Lenaz *et al., Biochim Biophys Acta* **2009**, *1787,* 384–392

2 Manda *et al., Curr. Chem. Biol.* **2009**, *3*, 342-366

3 Westerhoff, *Systems Biology: New Paradigms for Cell Biology and Drug Design*, Springer Berlin Heidelberg, **2007**, 45-67. Print

4 McLaughlin, *J. Nat. Prod.* **1999**, *62,* 504-540

5 Faber *et al. Eur. J. Org. Chem.* **2001**, 4537-4542