TOTAL SYNTHESIS OF SPHINGOLIPIDS AND SPHINGOSINE-TYPE SIGNALING MOLECULES OF MICROBIAL ORIGIN

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Choanoflagellates are unicellular eukaryotic organisms which can have a multicellular live stage. Intriguingly they are genetically the closest living relative to animals and therefore a popular model organism to study the evolution of multicellularity. The choanoflagellate *Salpingocea rosetta* develops rosettes upon feeding on prey bacteria *Algoriphagus machipongonensis* [1]. This led to the discovery of multicellularity inducing sulfonolipids (RIFs) [2], and a biosynthetically related competitive inhibitor molecule (IOR-1) produced by the same bacterial species [3]. To study the impact of such signaling molecules and their biological impact total synthesis and chemical modification has been the method of choice [4]. The first total syntheses of IOR-1 and RIF-1 confirmed the structure of IOR-1 [2, 3], however they were not suitable to study structure-activity relations (SAR) in detail and to identify the biological target in *S. rosetta*. Hence, we first established a more efficient and modular synthesis of the inhibitor IOR-1. Starting from a known tartaric acid derivative, we accomplished the synthesis in only 6 steps using a decarboxylative alkylation reaction as a key step. Using this short synthetic route, we synthesized more than 10 derivatives for detailed structure activity studies and chemical probes usable for the identification IOR-1´s biological target. Ongoing bioactivity studies will now provide a better understanding of the biochemical processes underlying the multicellular development and moreover the evolution of multicellular organisms.

[1] R. A. Alegado, L. W. Brown, S. Cao, R. K. Dermenjian, R. Zuzow, S. R. Fairclough, J. Clardy, N. King, *elife* **2012**, e00013.

[2] a) A. Woznica, A. M. Cantley, C. Beemelmanns, E. Freinkman, J. Clardy, N. King, *Proc. Nat. Acad. Sci.* **2016**, 113, 7894; b) C. Beemelmanns, A. Woznica, R. A. Alegado, A. M. Cantley, N. King, J. Clardy, *J. Am. Chem. Soc.* **2014**, 136, 10210.

[3] A. M. Cantley, A. Woznica, C. Beemelmanns, N. King, J. Clardy *J. Am. Chem. Soc.* **2016**, 138, 4326.

[4] D. Leichnitz, L. Raguž, C. Beemelmanns *Chem. Soc. Rev.* **2017**, 46, 6330.