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Organic Synthesis as a Scientific Method

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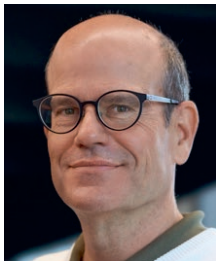
Abstract: Examples from our group on the use of organic synthesis as a scientific method are presented. Challenges regarding the constitution and configuration of natural products, their biological activity, the feasibility of biosynthetic transformations, the role of putative intermediates in biosynthetic pathways, and the role of substituents in toxic compounds have been investigated by the preparation of synthetic natural products and their derivatives.

Keywords: Chemical biology · Medicinal chemistry · Organic chemistry · Total synthesis



Karl Gademann grew up in Zurich and New York City, studied chemistry at ETH Zurich and received a PhD working with Prof. Dr. Dieter Seebach. Postdoctoral work at Harvard (Prof. Dr. Eric Jacobsen), and habilitation at ETH with Prof. Dr. Erick M. Carreira. Professorial appointments were held at EPFL, University of Basel, and University of Zurich. Industrial experience included CILAG/Janssen and Givaudan. Former service work includes research councilor at the Swiss National Science Foundation, head of the department at UZH, and dean of research in Basel. Karl Gademann is also strongly involved in charities and foundations supporting the next generation of scientists.

1. Introduction

The creation of new matter by synthesis represents the foundation of the chemical sciences.[1] As recognized 150 years ago, chemistry creates its own objects for study, which sets this discipline apart from many others.[2] This creative process and the generation of new chemical matter have thus directly impacted science and society, by the generation of new drugs, fabrics, materials, colors, fragrances, among many others.

There is one aspect of chemical synthesis though that might be nowadays often overlooked, yet it is critical to its impact in science. Chemical synthesis constitutes a scientific method that allows us to investigate science with excellent rigor, probing complex systems for example in biology or medicine with atomic resolution and molecular precision. This powerful approach has driven forward the discipline of organic chemistry since Wöhler's synthesis of urea.[3]

More recently, this very powerful and creative raison d'être for organic synthesis has been critically discussed by scholars comparing organic synthesis to an art (pour l'art) or even evoking Rutherford's comment on science beyond physics as stamp-collecting.[4] Furthermore, scientists make the case for total synthesis to remain a training ground for pharmaceutical industry.[5] The goal of this account is to showcase studies from our group's research in employing organic synthesis as a powerful scientific method.

I often get asked on how targets are selected for total synthesis. The answer is directly related to this article in that compounds are selected which pose fascinating questions related to their bioactivity, their mechanism of action, their biogenesis, and/or their structure and reactivity. In addition, compounds will be selected where synthesis can make an impact in its function as a scientific method, for example when compared to purely isolating more of the natural product from the source, which in many cases is not (easily) possible.

Our research program benefits through strong collaboration with many groups in biology, medicine, and material science, both within Switzerland and abroad. It is the portfolio of scientific methods and approaches that further leverages the power of organic synthesis as a scientific method.

In this account, selected examples will be discussed highlighting the role of organic synthesis in investigating; (1) chemical structure, (2) biological activity, (3) biogenetic hypotheses, (4) enzymatic pathways in bacterial biosynthesis, and (5) evolutionary aspects of toxin selection in primary producers such as cyanobacteria.

2. Chemical Synthesis as a Scientific Method

2.1 *Probing Chemical Structure and Biological Activity*

The glycosylated antibiotic fidaxomicin (**1**) heals patients in the clinic from *Clostridioides difficile* infections operating *via* the inhibition of transcription.[6] We have been the first group to achieve the total synthesis of this antibiotic,[7] and have over the last decade identified important features for activity,[8] in a few examples even surpassing the parent compound.[9] The mechanism of action is related to inhibition of RNA polymerase with no observed cross-resistance to the clinically used drugs of the rifamycin class.[10]

In contrast to fidaxomicin, mangrolide A (**2**) features different carbohydrate units on the same core resulting in a reportedly different biological mechanism *via* translation inhibition.[11] This fascinating hypothesis of evolutionary target switching (from RNA polymerase to the ribosome) *via* sugar exchange prompted us to evaluate it *via* chemical synthesis.[12] Challenges included the unusual amino-disaccharide and β-selective glycosylation on the sterically encumbered secondary OH group of the macrolactone. The disappointment was profound when we found a complete lack of antibiotic activity for mangrolide A,[12] in contrast to the claims in the patent![13] The related congener mangrolide D (**3**)[14] was also corrected[15] to the revised structure **4**: The presence of 4'-*epi*-vancosamine in **4** and not vancosamine itself was established by the preparation of both isomers. Salient features of the route included a Shibasaki reaction of enone **5** to enantiomerically enriched epoxide **6**, Pd-mediated allylic alkylation and ring closure to dihydropyranone **7**, intramolecular 1,4-N addition *via* oxazoline **8**, and subsequent introduction of the azide as a protected amine equivalent in **9**.[15] Glycoslation was enabled by the Au-catalyzed reaction of the alkyne donor **10** with the sterically

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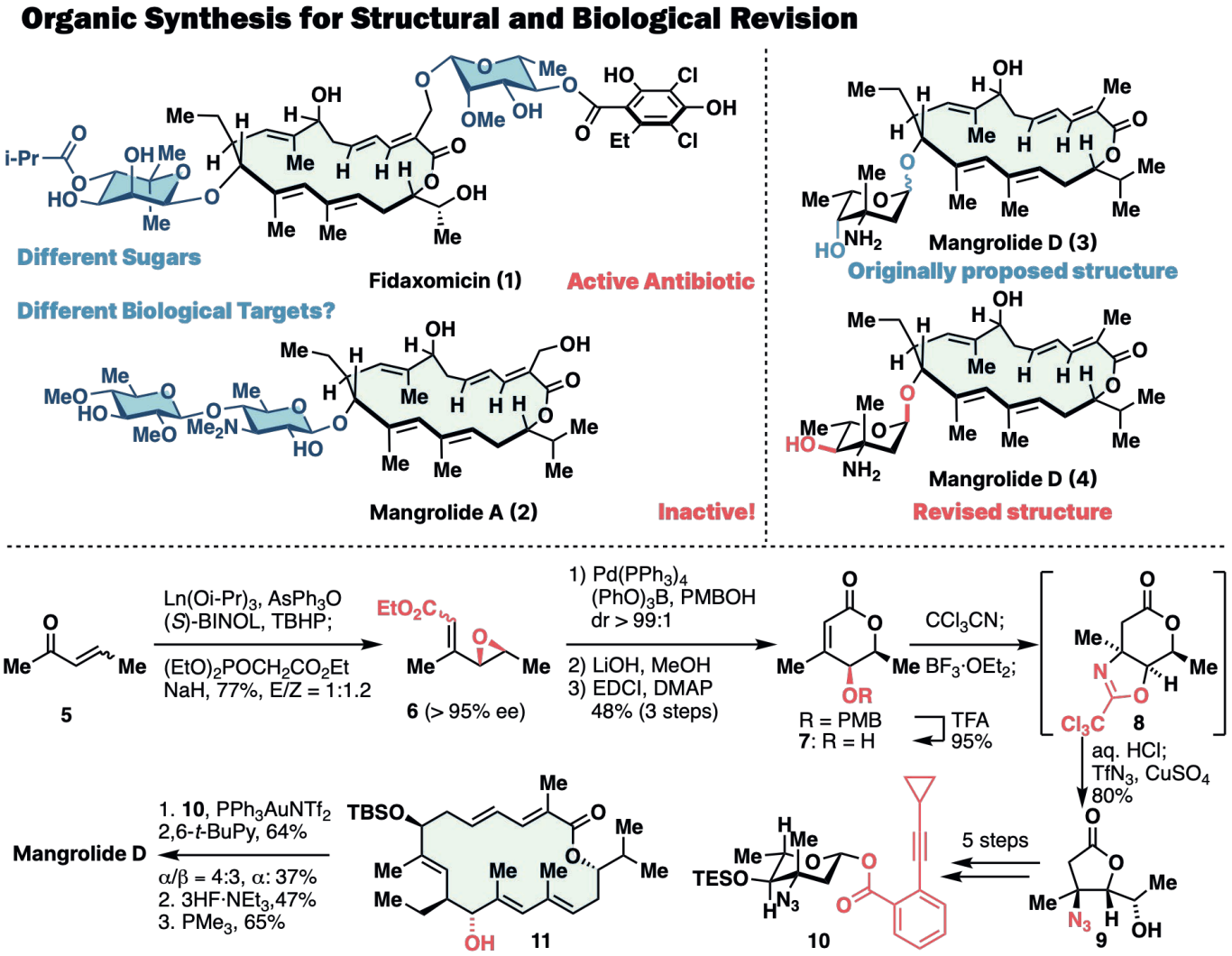
encumbered OH group in mactolactone **11**, and the use of the azide as a masked amino group proved to be essential throughout the synthesis (Scheme 1).[15]

2.2 Organic Synthesis Probing Biogenetic Hypotheses

Any biogenetic proposal starts with an evaluation of its chemical feasibility. Organic synthesis can provide a scientific approach to this problem – if a reaction can be observed in the laboratory, it can also in principle be observed in a natural system, even though reaction conditions might differ. These laboratory experiments demonstrate the feasibility of a potential hypersurface to reach products from a given set of starting materials. Pericyclic reactions have long been debated to be mediated by enzymes, and strong evidence was reported over the last two decades for biocatalytic transformations.[16] In addition, 'biomimetic syntheses' often appeal for their brevity and elegance. In the context of our work on terpenoids,[17] we have developed a synthetic access to C_{40} dimeric terpenoids called obtusinones D (**12**) and E (**13**).[18] Oxidation of brussonol (**14**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the corresponding quinone, which reacted in a [4+2] hetero Diels-Alder reaction to the target compounds. X-Ray crystal structure analysis of **12** confirmed its structure and therefore necessitated a structural reassignment of the originally proposed *endo* isomers of **12** and **13**. Consequently, organic synthesis established the feasibility of this transformation and corrected the scientific record (Scheme 2, top).

In a different project, we were intrigued by the biosynthetic proposal for periconianone A (**15**) featuring a late-stage, intramolecular aldol reaction between C(4) and C(12) in the dienetrione precursor **16**.[19] Such reactions are considered rare in terpenoids, and the presence of the tertiary OH group and the possibility of a retro aldol reaction further warranted synthetic investigations of its feasibility.[20] The intermediate **17** was transformed *via* a ketol rearrangement to enone **18** mediated by a Ca salt, an unusual base for this reaction. The formation of the thermodynamically more stable enone was considered as the driving force in this equilibrium. The key aldol reaction of **19** was then investigated, and a variety of Lewis and Brønsted acids were investigated without success, as either propanal was liberated or elimination of the tertiary OH was observed. Finally, the use of diphenylphosphate in toluene resulted in the clean formation of the aldol product **20** in 71% yield and excellent diastereoselectivity. Elaboration to the natural product *via* α-selenation and elimination established the successful synthesis of periconianone A (**15**) and the chemical feasibility of this unusual aldol reaction (Scheme 2, middle).

The use of calcium methoxide as a base in the ketol rearrangement prompted us to postulate and to investigate biosynthetic relationships *via* such a pathway. Microsphaeropsisin B (**21**) and periconianone C (**22**) differ in the position of the dihydroxyfuran ring that appears attached in a shuffled way to the decalin framework in both natural products. We postulated a hypothesis that an α-ketol rearrangement *via* an opened α-hydroxyketone could connect both natural products.[21] Gratifyingly, we were able to



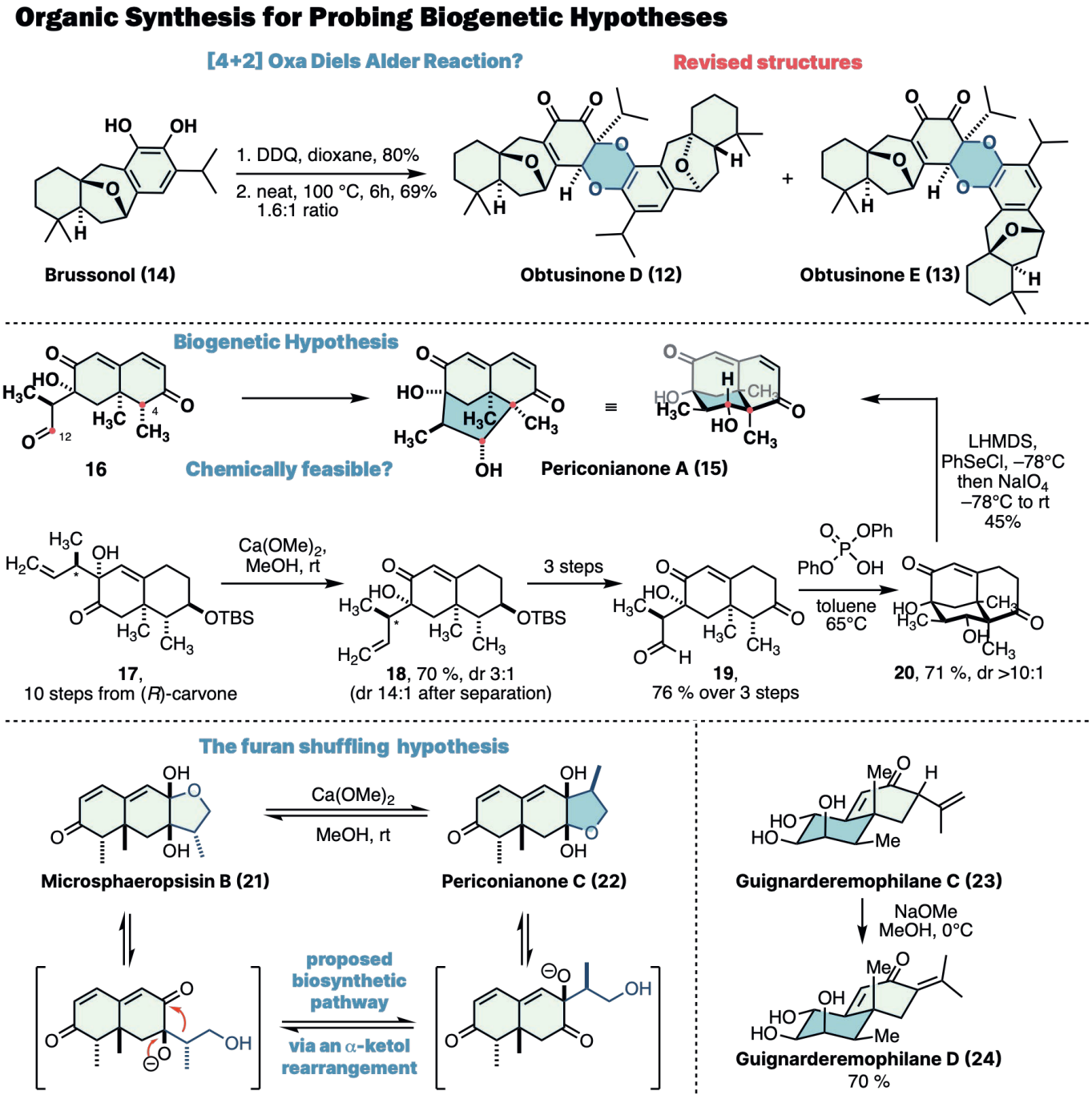
Scheme 1. Organic synthesis for structural and biological revision in the Fidaxomicin and Mangrolide Series.

validate this hypothesis in the laboratory, simply by exposing each of the purified, synthetic natural products to the Ca base.[21]

Complementing these studies on eremophilane diterpenoids, we have also developed synthetic access to guignarderemophilanes C and D. The establishment of the triol unit posed significant challenges, and the use of a tethering Si protecting group proved to be key to their preparation. Isomerization of congener C (**23**) to congener D (**24**), mediated by base, completed the synthesis (Scheme 2, bottom).[22]

2.3 *Probing Enzymatic Pathways in Biosynthesis*

The *ham* cluster in *Burkholderia* produces two distinct secondary metabolites, the (–)-fragin and the racemic valdiazen.[23] We have demonstrated that the latter compound as well as the related leucine derived leudiazen[24] function as signaling molecules in bacteria, regulating the expression of dozens of genes.[23,24] On the biosynthesis side, the *ham* gene cluster is interesting as the biosynthesis is stereodivergent in operation, in that resulting from one cluster, both enantiopure (–)-fragin and racemic valdiazen are observed. We postulated that enantiomerically pure and naturally occurring L-valine is converted to the biosynthetic end products *via* a dihydrosydnone N-oxide.[25] This unusual heterocyclic structure is related to Traube's anion, the clinically used drug molsidomin, and bears the name of its city of origin, Sydney. We prepared ^{15}N labelled dihydrosydnone N-oxide as well as valdiazen using 1 M aq. HCl and $Na^{15}NO_2$ from the corresponding hydroxylamine precursor, the preferred method for the isotopically labelled compounds, whereas isoamyl nitrite was found useful for the non-labelled diazeniumdiolates.[25] Feeding these compounds to bacteria carrying selected knock-out mutations in the gene cluster and analyses by high-performance liquid chromatography-high-resolution tandem mass spectrometry (HPLC-HRMS-HRMS)

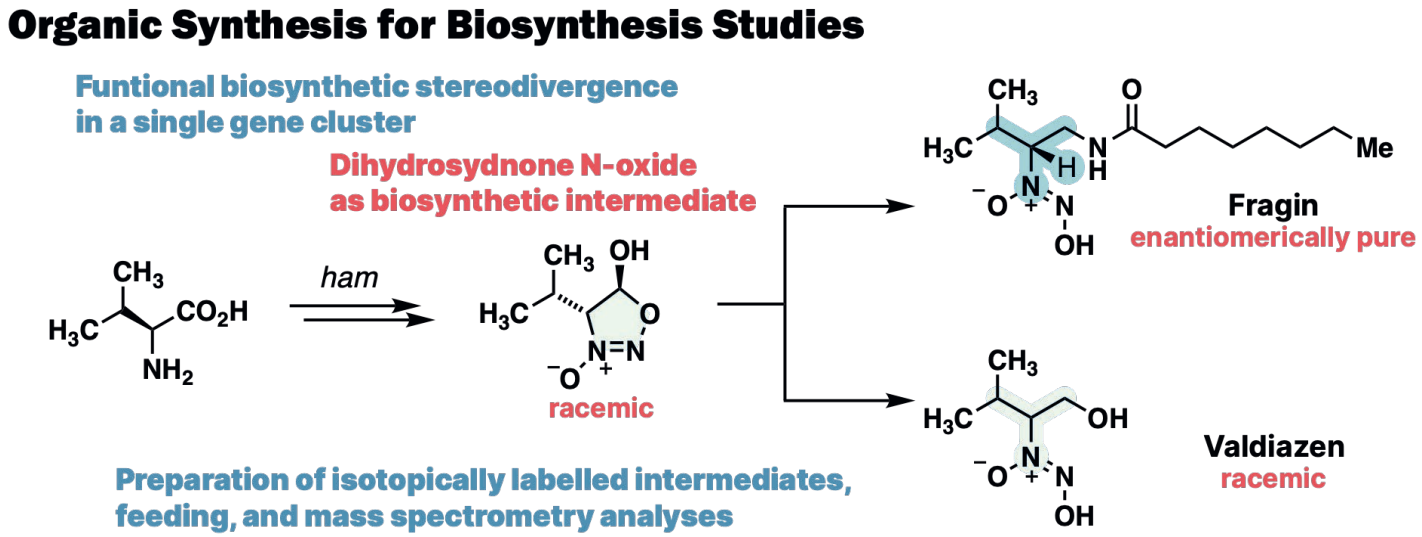


Scheme 2. Probing biogenetic hypotheses by chemical synthesis.

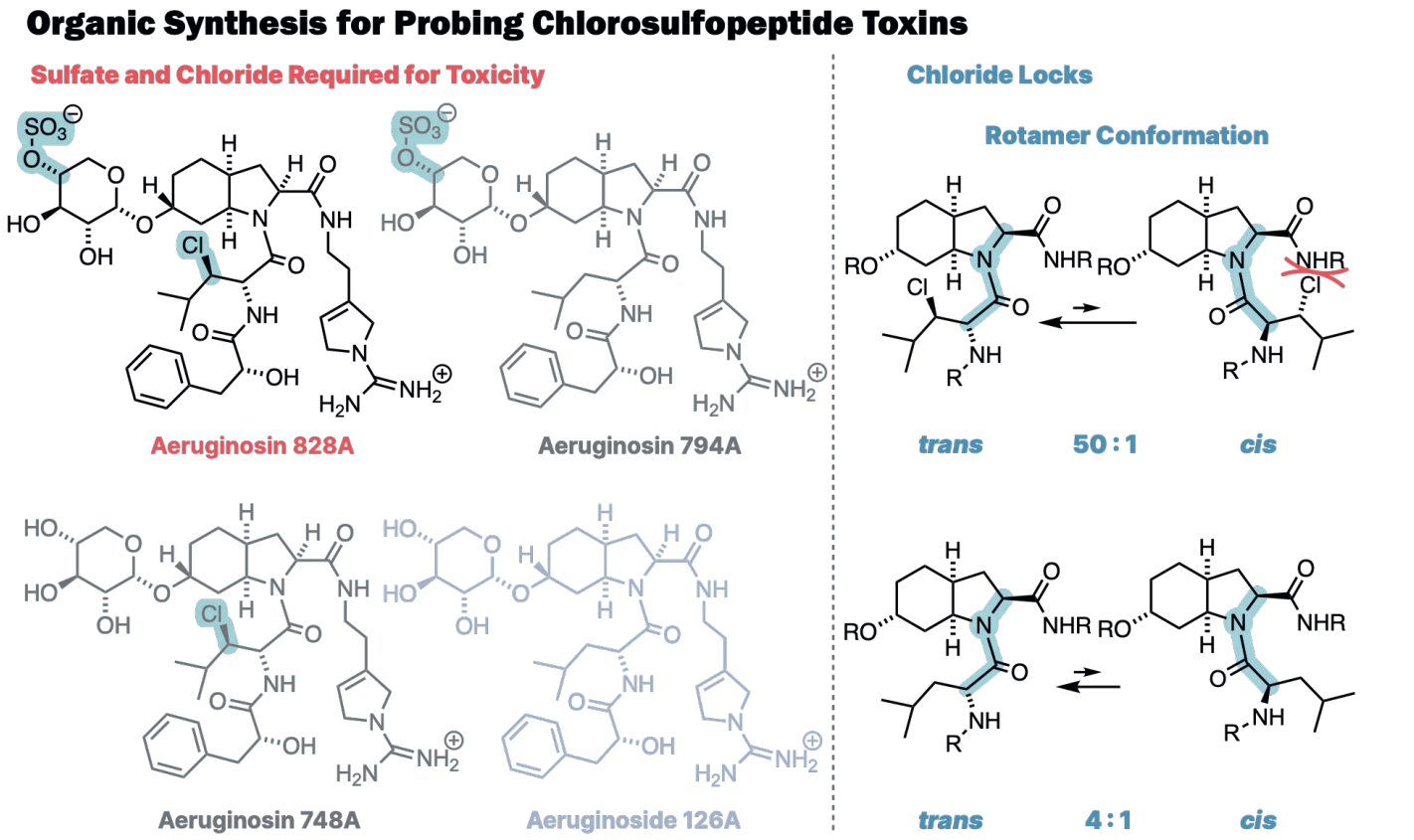
then allowed us to demonstrate that indeed this dihydrosydnone N-oxide constitutes a competent biosynthetic intermediate.[25] In addition, we provided evidence that the subsequent reductive amination in the bacterial biosynthesis is stereoselective.[25] By providing isotopically labelled putative biosynthetic intermediates, organic synthesis serves as a powerful method to investigate the biogenesis and the unusual stereodivergence in the *ham* cluster (Scheme 3).[25]

2.4 *Probing Toxicology by Chemical Synthesis*

Cyanobacteria constitute important primary producers of biomass *via* oxygenic photosynthesis. Consequently, evolutionary pressure from grazers resulted in the selection of toxic secondary metabolites,[26] which have been postulated to reduce grazing pressure. Climate change, population overgrowth, and eutrophication all may contribute to harmful algal growth, which is becoming more prevalent on a global scale. In collaboration with the group of Prof. Jüttner and Dr. Blom at the limnological station at UZH,[27] we have investigated a series of metabolite families beyond the regulated toxin microcystin from cyanobacteria and established their role as toxins against grazers, and potentially against mammals and humans.[27] An interesting class of compounds are the aeruginosins such as the 828A congener,[28] which feature a central L-2-carboxy-6-octahydroindole unit with a 1-(N-amidino-Δ^3-pyrrolino)ethyl moiety attached. The central hypothesis to be investigated was that cyanobacteria devoid of



Scheme 3. An unusual biosynthetic intermediate in a stereodivergent biogenesis from a single gene cluster.



Scheme 4. Probing toxicity of chlorosulfopeptides with organic synthesis.

the prototype toxin microcystin restore toxicity by the generation of both sulfated and chlorinated compounds such as aeruginosin 828A, whereas the microcystin-producing strains feature the less toxic aeruginoside 126A.[28] Chemical synthesis was the key scientific method of choice, as contamination by other toxins during the isolation procedure cannot be ruled out. The synthesis of all four congeners was highly convergent, with each of the building blocks accessed in 5–11 steps and aeruginosin 828A in 18 steps longest linear sequence.[29] Toxicity assessment against the freshwater crustacean *Thamnnocephalus platyurus* revealed multiple interesting conclusions: (1) Both Cl and sulfate groups infer toxicity, (2) chlorosulfopeptides complement toxicity in microcystin deficient strains; (3) the Cl substituent locks the amide rotamer in the *trans* configuration, and (4) toxicity in cyanobacteria should be evaluated beyond microcystin. Taken together, chemical synthesis of chlorosulfopeptide toxins was key in mapping out structural features for toxicity while ruling out contamination with natural toxins.[29]

3. Conclusion

This account presented research from our group demonstrating how organic synthesis is applied as a scientific method. The applications of organic synthesis to address purely chemical challenges related to constitution and configuration, biochemical questions such as the fitness of postulated structures in biosynthesis, and biological and toxicological hypotheses were discussed. The usefulness of organic synthesis in such endeavors is beyond doubt due to its ultimate experimental rigor and atomistic precision. Drawbacks include the sometimes time-demanding nature of research projects, which however, can also be regarded as an opportunity for further, seemingly unrelated scientific discovery along with Eschenmoser's ideal of encountering new reactivity in pursuing complex molecular architecture.[30]

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