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Original title in the *Nachrichten aus der Chemie (Journal of the German Chemical Society GDCh)*:

"*Nicht essen, nur schauen – polyhalogenierte Naturstoffe aus Algen*"

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Beautiful but Toxic – Polyhalogenated Natural Products from Algae

Abstract

Certain micro algae produce so-called sulfolipids, a class of polychlorinated natural products. Consumption of these cell toxins by humans by means of mussels and shell fish can cause seafood poisoning. The rich stereochemistry and structural complexity of these natural products makes their synthesis challenging. Recent reports allow for an insight into the function and mechanism of action of sulfolipids in nature.

Like phospholipids, chloro-sulfolipids consist of non-polar lipophilic and polar hydrophilic moieties (Figure 1 **A**).[1] As lipophilic portions serve poly-halogenated alkyl residues, whilst hydrophilicity is ensured by charged sulfonate groups.

Sulfolipids especially occur in membranes of certain micro algae such as found in the adriatic see. For example, *Danicalipin A* (**1**) is the main component of the cell membrane of *Ochromonas danica*. It is mainly located in the whip-like extension of this golden brown micro algae. This so-called flagella are crucial for the locomotion of single-cell organisms.

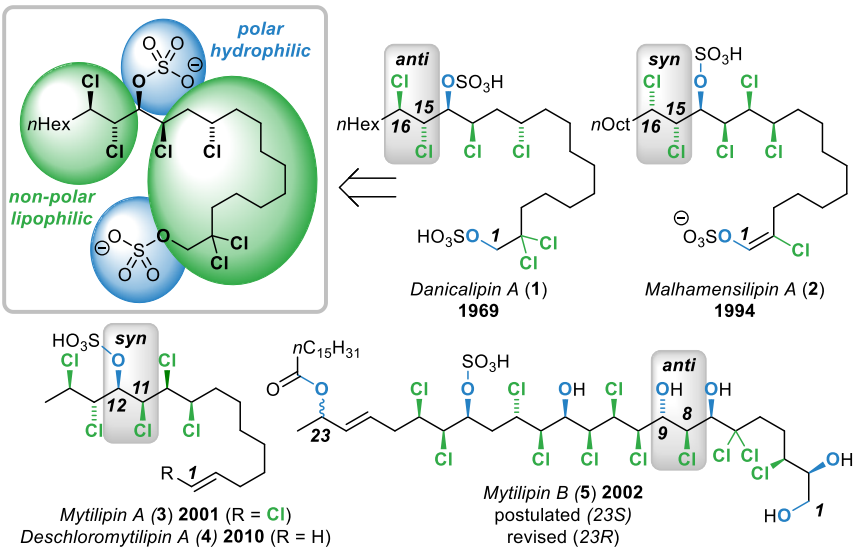


Figure 1. Exemplary structures of sulfolipids, as found in marine and fresh water environments.

Sulfolipids are cytotoxic, anti-microbial and anti-proliferative. In particular, the natural products **3**, **4** and **5** can cause life-threatening shell fish food poisoning. On the first glance it surprises that primarily water organisms produce these natural products. Chloro alkanes are known as highly reactive electrophiles, which are prone to hydrolysis yielding alcohols. In contrast, aliphatic alkyl chlorides such as in sulfolipids and the artificial sweetener sucralose are much less reactive. Alkylation reactions are most likely not responsible for the bioactivities of these natural product family.

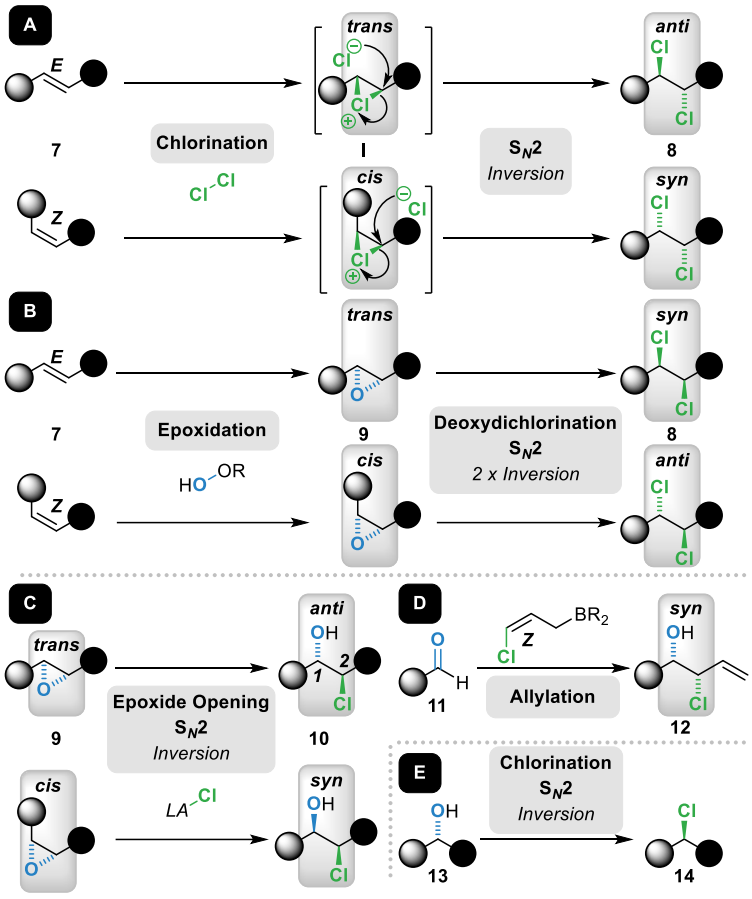
Characteristic for sulfolipids are Cl-atoms attached to adjacent carbon atoms bearing chirality centres, a structural motif which is referred to as 1,2- or *vicinal* Dichloride. Frequently, also OH-functions are incorporated. Through the neighbouring stereocentres *anti*- and *syn*-stereoisomers can be differentiated.

The high density of stereogenic centres impedes the synthesis of this target molecules. For the stereoselective preparation of chloro alkanes only a few methods have been described. This complicates the synthesis of members of this natural product family even further and might explain, why the first total synthesis has been reported four decades after the initial discovery.

In fact, total syntheses allow to verify - or often revise - the initially after isolation proposed structure. In addition, larger compound amounts are provided for further biological studies to rationalize their mode of action. Eventually, the preparation of related derivatives allows to establish a structure activity relationship.

Synthetic Methods

For the synthesis of sulfolipids especially chlorinations of alkanes **7** have been exploited, which afford dichlorides **8** (Scheme 2 **A**).[1] In the beginning, a chloronium ion of type **I** is formed as intermediate. While *E*-configured alkenes give rise of *trans*-heterocycle **I**, the *Z*-stereoisomers of **7** furnish *cis*-chloriranium cations **I**. Then, a S_N2-type attack of the chloride counterion from the backside leads to *syn*- and *anti*-1,2-dichlorides of type **8**, respectively. Therefore, the double bond configuration of the starting material **7** determines, which isomer of **8** is generated.



Scheme 1. Strategies for the synthesis of chlorine containing motifs (LA = *Lewis* Acid, S_N2 = bimolecular nucleophilic substitution).

However, the absolute configuration of the new chirality centres is difficult to control. To this end, only a few methods have been introduced for the asymmetric synthesis of vicinal dichlorides. As an alternative approach, compounds of type **8** are also accessible by alkene epoxidation and subsequent dichlorination in two steps (Scheme 1 **B**). For the enantioselective synthesis of epoxides **9** from alkenes numerous protocols have been described. The geometry of the starting olefins has a significant impact on the relative configuration of 1,2-dichloro alkanes **8**, too. Typically, the transformation of **9** into dichloro alkanes **8** proceeds under inversion with respect to both stereocentres. As a consequence, *Z*-alkenes furnish *anti*-dichlorides, whilst the *E*-counterparts enable the production of the *syn*-diastereoisomers of **8**.

1-Chloro-2-hydroxy alkanes of type **10** have mainly been prepared by means of ring opening of epoxides **9** using chlorine containing *Lewis* acids (Scheme 1 **C**). Also in this case, the configuration of epoxide **9** influences, which stereoisomer is predominantly formed. The allylation of aldehydes **11** with the aid of *Z*-3-chloro allylboranes enables the synthesis of *syn*-3-chloro-4-hydroxy-1-alkenes (**12**), whereby the carbon scaffold is extended by three further atoms (Scheme 1 **D**). Occasionally, conversions of alcohols **13** into chloro alkanes **14** under stereochemical inversion have been employed in the context of sulfolipid synthesis.

The absolute configuration of novel stereocentres cannot only be controlled by chiral catalysts and reagents, respectively. Also chirality centres of the starting materials in close proximity have an influence. In the following, applications of the delineated general strategies are showcased via selected synthesis of sulfolipids. Therein, methods are highlighted by the capital letters **A**, **B**, **C** and **D** in reference to Scheme 1. The numbers of carbon atoms refer to the respective target natural product (see Figure 1).

Mytilipin A and Neighbouring Group Effects

The first total synthesis of a sulfolipid has been reported by the group of *Carreira* in 2009 (Scheme 2).[2] At the outset, ethyl sorbate **15** was chlorinated at C-13 and C-14 in high levels of regio- and diastereoselectively (according to method **A** in Scheme 1). In the following, a three step sequence commencing from *anti*-dichloride **16** furnished the labile aldehyde **17**, in which the stereo centres on C-12 and C-11 had been established. Then, a *Z*-selective *Wittig*-reaction afforded alkene **18** under elongation of the carbon chain by eight carbon atoms.

Surprisingly, the ring opening of the epoxide **18** with the *Lewis* acid proceeded under retention of the configuration at C-11 (compare strategy **C** in Scheme 1). This observation has been rationalized by a neighbouring group effect of the proximal chlorine atom[3] on C-14, which results in formation of the five-membered chlorolium ion **III** under inversion at C-11. A second inversion on C-11 by means of nucleophilic substitution with the chloride counterion impacts an overall retention.

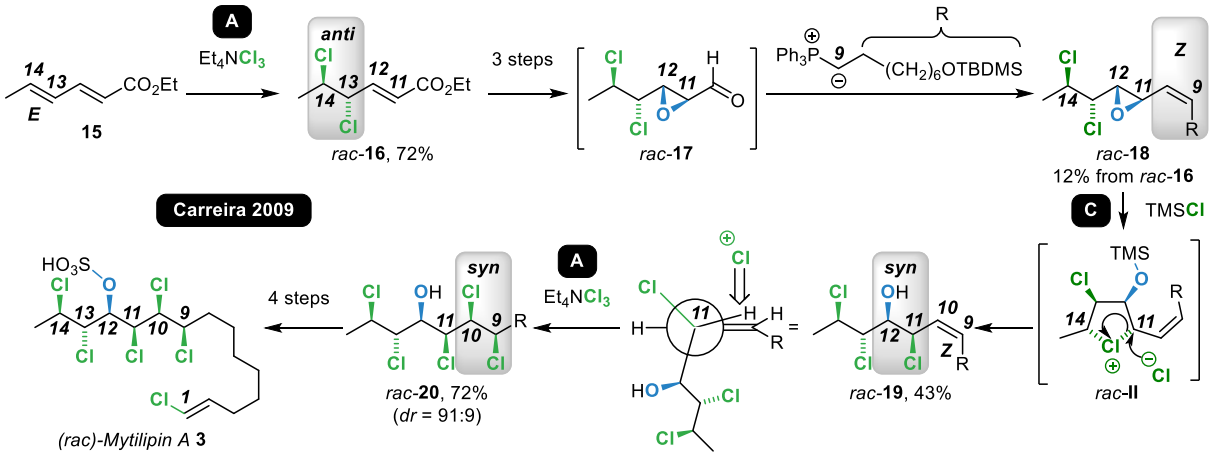
Indeed, such neighbouring group effects were observed in many syntheses of polyhalogenated natural products. As demonstrated by the group of *Vanderwal*,[4] certain reaction conditions can supress the effect of adjoined Cl-atoms.

Carreira and co-workers continued their synthesis through chlorination of the C-9/C-10 double bond (compare Scheme 1 **A**). Herein, the chirality centre on C-11 is crucial for the absolute configuration at C-10. Due to the *Z*-configuration of **19** the *syn*-stereoisomer of **20** is generated predominantly. Eventually, four additional synthetic manipulations lead to racemic *Mytilipin A*. This first synthesis comprised 11 linear steps. The first enantioselective synthesis of a chlorosulfolipid, which provided *Malhamensilipin A*, has been reported by the group of *Vanderwal*.[4b]

How to Determine Configurations

In fact, the determination of the three dimensional arrangement of the Cl- and OH-substituents of sulfolipids is challenging, since these natural products are acyclic. *Carreira* and co-workers developed a method to predict the relative configuration of adjacent chirality centres by means of NMR-coupling constants.[3a] Therefore, a database was established based on NMR-spectra and crystal structures of a set of representative model compounds.

Enabeled by an enantioselective chlorination of *E*-crotyl alcohol (**21**) with a chiral titanium catalyst, *Burns* and co-workers synthesized the enantiomer of *Deschloromytilipin A* (Scheme 3, above).[5] Transformation of dichloro alkane **23** via oxidation to the respective aldeyhde using reagent **24** and subsequent chloroallylation gave rise of alkene **26**. In the latter step, chiral *iso*-camphyl residues on the boron atom of allylation reagent **25** allowed to improve the stereoselectivity in terms of C-12.

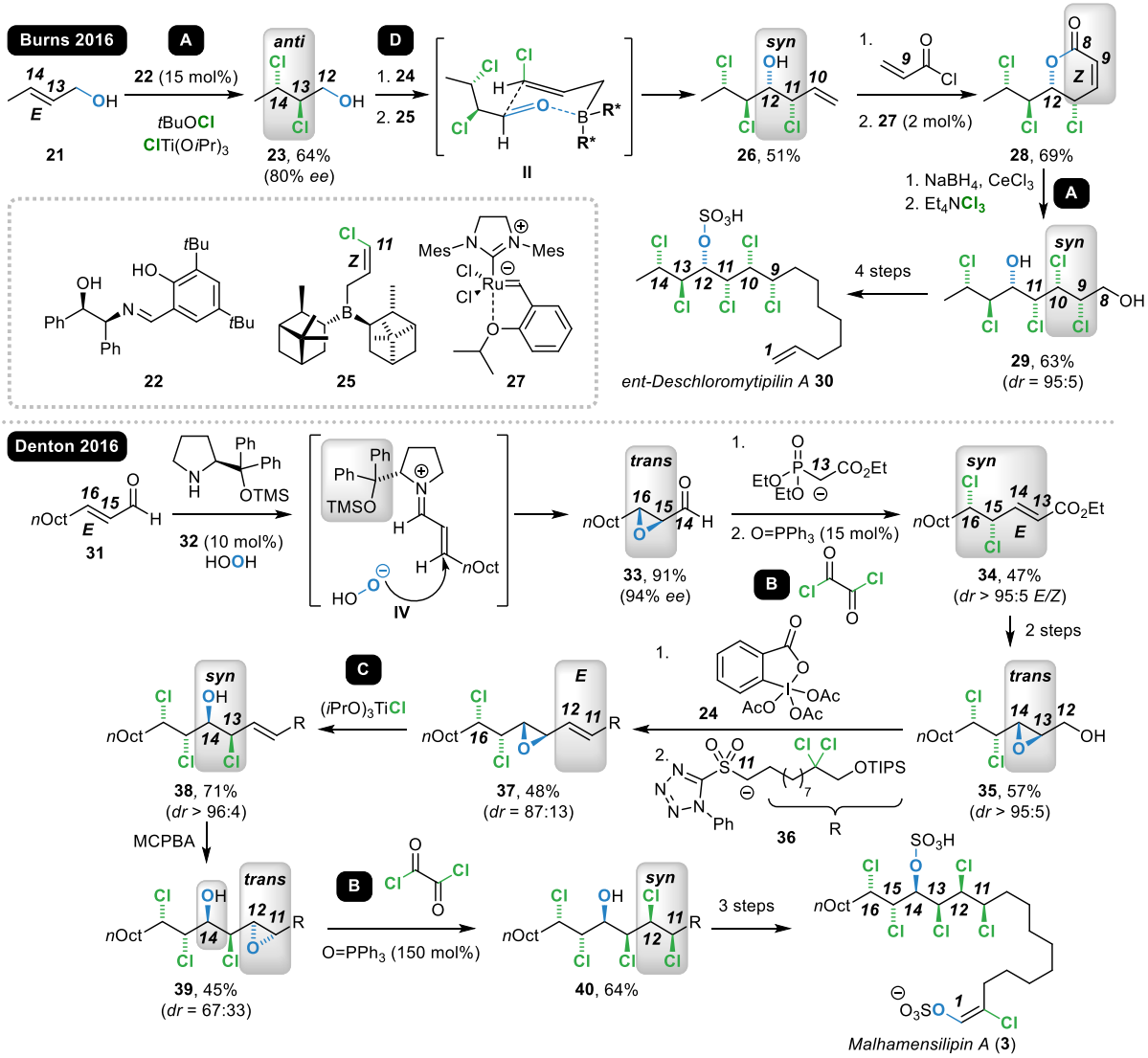


Scheme 2. Synthesis of *Mytilipin A* according to *Carreira* (*rac* = racemic, TBDMS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, *dr* = diasteromeric ratio).

Esterification of the OH-group at C-12 with acrylic acid chloride and ring closing metathesis using pre-catalyst **27** furnished the thermodynamical preferred *Z*-configured lactone **28**. In the following, chemoselective reduction of the ester function and diastereoselective chlorination controlled by the stereogenic centre at C-11 afforded pentachlorodiol **29**. In four further synthetic transformations *ent-Dechloromytilipin A* (**30**) was obtained in eleven steps overall.

How to Introduce Chlorine Atoms

The synthesis of *Malhamensilipin A* has been accomplished by the group of *Denton* based on deoxydichlorinations of epoxides according to Scheme 1 **B** to introduce Cl-atoms (Scheme 3, below).[6] In the beginning, the stereo centres at C-16 and C-15 were defined through an asymmetric epoxidation of aldehyde **31** applying *Jørgonson´s* prolinol **32** as catalyst via iminium intermediate **IV**. Afterwards, *Horner-Wadsworth-Emmons*-alkenylation and triphenylphosphine oxide promoted chlorination allowed to access *E*-Alkene **34**. Reduction of the ester moiety and diastereoselective *Sharpless*-epoxidation facilitated the assembly of the stereo centres at C-13 and C-14 of primary alcohol **35**. Oxidation with the aid of *Dess-Martin*-reagent **24** and *E*-selective *Julia-Kociensky*-alkenylation engaging sulfone **36** allow to complete the carbon skeleton of the target natural product. Next, treatment of **37** with the *Lewis* acid Ti(O*i*Pr)$_3$Cl effects epoxide opening in allylic position at C-13.



Scheme 3. Synthesis of *ent-Deschloromytilipin A* according to *Burns* (above) and of *Malhamensilipin A* by *Denton* (below, *t*Bu = *tert*-butyl, *n*Oct = *n*-octyl, *i*Pr = *iso*-propyl, MCPBA = *meta*-chloroperoxybenzoic acid).

The stereochemical retention was explained by the neighbouring group effect of the Cl-atom at C-16. Epoxidation with the achiral peroxy acid MCPBA in moderate stereoselectivity (*dr* = 67:33) and catalytic dichlorination of **39** provided pentachloro alcohol **40**. In the end, three further synthetic operations finalize the total synthesis of *Malhamensilipin A*. Remarkably, the sterically encumbered hydroxyl group on C-14 was not affected in the conversion of **39** to **40**.

For the synthesis of *Danicalipin A* (**1**) and *Mytilipin A* (**3**) *Yoshimitsu, Umezawa* and *Matsuda* utilized mainly transformations of epoxides into 1,2-dichlorides and of alcohols into alkyl chlorides to introduce chlorine atoms (compare Scheme 1 **C** and **E**).[7]

Insight Facilitated by Total Syntheses

Total syntheses enabled the determination of the absolute and relative configuration of *Mytilipin A* (**3**)[2,7a] and *Danicalipin A* (**1**).[4a] In the case of *Malhamensilipin A* (**2**), syntheses verified that the original structure elucidation lacked one sulfonyl group[8] and verified the proposed configuration.[4b]

The synthesis of the proposed structure of *Mytilipin B* (**5**) indicated that the configuration at C-23 has been assigned incorrectly.[9] Biological studies with synthetic samples of *Danicalipin A* (**1**) and derivatives showed that:
(1) Both, the chlorine atoms and the sulfonyl groups are crucial for the cytotoxicity and the enhanced cell permeability.[10]
(2) While the relative configuration, which impacts the preferred confirmation, is essential for the cell permeability, it has a little effect on the cytotoxicity.[11]
(3) The absolute configuration in contrast has no influence on the toxicity.[7a]
(4) Substitution of the Cl- through Br-atoms has virtually no effect on the bioactivity. A derivative with fluorine instead of chlorine atoms was significantly less toxic.[12]
Since both *Danicalipin A* derivatives possess the same preferred confirmation, this result has been rationalized by the decreased lipophilicity of the fluorinated analogue. Based on these results, the *Carreira* group proposed that *Danicalipin A* increases the mobility of the flagella of the micro algae *Ochromonas Danica* to facilitate movement.[11] Synthetic samples of other representatives of this remarkable natural product family have not been assessed on their bioactivities.

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During the revision of the current article Carreira reported on the revised structure of Mytilipin B elucidated through total

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Peter Huy, born 1980, is leading a young researcher´s group as a *Liebig* fellow at the Saarland University since 2014. He pursued his PhD thesis in organic chemistry in the group of Prof. Hans-Guenther Schmalz at the University of Cologne. Subsequently, he joined the group of Prof. Ari Koskinen at the Aalto University in Helsinki and the group of Prof. Ben List at the Max-Planck Institute for Carbon Research in Muehlheim at Ruhr as a postdoctoral researcher. His research interests are committed towards homogenous catalysis and natural product synthesis. In the preparation of the current manuscript, he was supported by his bachelor student **Philipp Grewelinger**.