Doctoral Thesis

Enabling tactics and strategies to access polychlorinated hydrocarbons
total synthesis of chlorosulfolipids and insights into their chemistry

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Enabling Tactics and Strategies to Access Polychlorinated Hydrocarbons -
Total Synthesis of Chlorosulfolipids and Insights into Their Chemistry

A dissertation submitted to the

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presented by

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Abstract

Chlorosulfolipids, which were first discovered in the late 1960’s by ELOVSON and VAGELOS, represent an unusual class of chlorinated natural products originating from microalgae (Chart I). Until today little is known about the natural function of these entities, their role in the membranes of the producing organisms and their biological activity. Importantly, in view of the fact that a few of them have been isolated from Mediterranean mussels, in which the microalgae accumulate, questions about their toxicity for humans and their mode(s) of action are raised. Since many chlorosulfolipids have been isolated only in minute amounts from natural sources, the investigation of synthetic approaches is warranted to address these issues. This doctoral thesis presents the development of tactics and strategies to access chlorosulfolipids, leading to the first total synthesis of a chlorosulfolipid, hexachlorosulfolipid A, and some interesting discoveries concerning the chemical reactivity of such polychlorinated entities.

Chart I: Hexachlorosulfolipid A (I) and undecachlorosulfolipid A (II), two representative chlorosulfolipids.

Reliable spectroscopic methods for the configurational assignment of intermediates en route to chlorosulfolipids are of utmost importance in any synthetic effort. Hence, this thesis first focuses on the validation of J-based configuration analysis (JBCA) for chlorinated systems. JBCA, an NMR-spectroscopic method established by MURATA and coworkers for polyketide natural products, is based on the analysis of homo- and heteronuclear coupling constant patterns between two stereogenic centers; however, reference values for coupling constants as a function of the dihedral angle were lacking for chlorinated systems. This previously existing gap was filled by the preparation and thorough NMR-spectroscopic investigation of a collection of crystalline trichlorohexanediols (VI and VII), prepared by ZrCl$_4$- and TiCl(OiPr)$_4$-mediated epoxide openings of the corresponding epoxycarboxylalcohols (IV and V) (Figure I). The latter were prepared in a few steps from commercially available ethyl sorbate (III). Additionally, a detailed conformational analysis of these compounds is presented.
Subsequently, the total synthesis of hexachlorosulfolipid A (I) was addressed. The linear sequence presented herein starts from ethyl sorbate (III) and leads to the targeted chlorosulfolipid in 10 steps and 1.4 % overall yield, corresponding to 65 % average yield per step (Scheme I). A key observation of our synthetic investigations is a retentive epoxide opening of VIII with trimethylsilyl chloride, explicable by the formation of a presumably five-membered chloronium intermediate. The approach developed represents the first total synthesis of a chlorosulfolipid that has been reported.

After the successful synthesis of hexachlorosulfolipid A (I) the total synthesis of undecachlorosulfolipid A (II) was investigated (Scheme II). The C_{11-13} fragment (XIII) (natural product numbering) was prepared in 17 steps and 0.7 % overall yield (longest linear sequence) starting from S-1,2,4-butanetriol (XI) (Scheme IIa) and subsequently coupled with the C_{14-23} fragment (XIV) in a Z-selective JULIA-KOCIEŃSKI-coupling (Scheme IIb). Further modifications include an invertive epoxide opening using triphenylphosphine dichloride, diastereoselective dichlorination, a regioselective MARTIN-dehydration to install the C_{2-3} double bond, chemoselective esterification and protective group manipulations. In preliminary experiments, ester XVI was transformed into its monosulfate and subsequently subjected to acetonide hydrolysis conditions. Mass spectrometric analysis of the product suggests the successful completion of the synthesis.
Scheme II: Investigations towards the total synthesis of undecachlorosulfolipid A (II).

With the synthesis and biological evaluation of analogs of the natural products atpenin A5 (XVII) and leukotoxindiol (XX) preliminary studies were carried out to shed some light on the role of chlorides in natural products (Chart II). Based on the hypothesis that the chlorides have the purpose to destabilize undesired conformations in much the same way as methyl- and hydroxyl substitution leads to well defined conformations of polyketides, the idea was developed to interchange chloride and methyl groups and chloride and hydroxyl groups and investigate whether the biological activity of the resulting analog is comparable to the activity of the parent natural product. For the examples examined, atpenin A5 (complex II inhibitory activity) and leukotoxindiol (cytotoxicity for HepG2 cells), this proved to be the case.

Chart II: Atpenin A5 (XVII), leukotoxindiol (XX), and their prepared and biologically evaluated Me- and Cl-analogs.

Abbildung I: Hexachlorosulfolipid A (I) und Undecachlorosulfolipid A (II), zwei repräsentative Chlorosulfolipide.

Abbildung II: Validierung der J-basierten Konfigurationsanalyse für chlorierte Systeme durch Synthese von kristallinen Trichlorohexandiolein (a) und NMR-spektroskopische Analyse ihrer homo- und heteronuklearen Kopplungskonstanten (b).

Daraufhin wurde die Totalsynthese von Hexachlorosulfolipid A (I) untersucht. Die hier präsentierte lineare Synthesesequenz beginnt mit Ethylsorbat (III) und führt in 10 Schritten und 1.4 % Gesamtausbeute zum Zielmolekül, was einer durchschnittlichen Ausbeute von 65 % pro Schritt entspricht (Abbildung III). Eine Schlüsselbeobachtung der Untersuchungen ist eine retentive Öffnung des Epoxids VIII mit Trimethylsilylchlorid. Diese Synthese stellt die erste Totalsynthese eines Chlorosulfolipids überhaupt dar.

Abbildung III: Totalsynthese von Hexachlorosulfolipid A (I).

Durch die Synthese und biologische Evaluation von Analoga der Naturstoffe Atpenin A5 (XVII) und Leukotoxindiol (XX) sind einige vorläufige Studien durchgeführt worden, um die Rolle von Chloriden in Naturstoffen zu beleuchten (Abbildung V). Basierend auf der Hypothese, dass Chloride den Zweck haben, unerwünschte Konformationen zu destabilisieren, genauso wie Methyl- und Hydroxylgruppen zu definierteren Konformationen der Polyketide führen, wurde die Idee entwickelt, Chloride und Methylgruppen sowie Chloride und Hydroxylgruppen in Naturstoffen gegen einander auszutauschen und zu untersuchen, ob die biologische Aktivität mit der des Naturstoffes selbst vergleichbar ist. Tatsächlich wurde für die beiden untersuchten Beispiele, Atpenin A5 (Komplex II Inhibition) und Leukotoxindiol (Cytotoxizität für HepG2-Zellen), gefunden, dass eben dies der Fall ist.

Abbildung V: Atpenin A5 (XVII), Leukotoxindiol (XX) und synthetisierte und biologisch untersuchte Me- und Cl-Analoga.