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A Concise Enantioselective Synthesis of the Chlorosulfolipid Malhamensilipin A

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The chlorosulfolipids (**1**−**5**, Figure 1)[1−3] are a fascinating class of natural products that, after decades of inattention from organic chemists, have recently garnered interest as targets of synthesis[4,5] and inspired methodology for stereoselective chlorination.[6−8] In early 2009, the Carreira group published the synthesis of mussel toxin chlorosulfolipid **3**, representing the first synthesis in this class.[4] Shortly thereafter, our laboratories disclosed the NMR-based relative and absolute stereochemical elucidation of algae-derived lipid danicalipin A (**1**), which was supported by a concise synthesis.[5] Recently, we reported the structural revision and stereochemical determination of the protein tyrosine kinase inhibitor malhamensilipin A (**2**), a chlorosulfolipid related to danicalipin A that is produced by the alga *Poterioochromonas malhamensis*.[2b] In this communication, we describe a stereocontrolled and concise synthesis of malhamensilipin A that constitutes the first enantioselective synthesis of a chlorosulfolipid. Our synthesis features a selective, base-mediated elimination of HCl from a penultimate intermediate bearing seven chlorine atoms and two sulfate groups as the final step to introduce the unique (*E*)-chlorovinyl sulfate functional group.

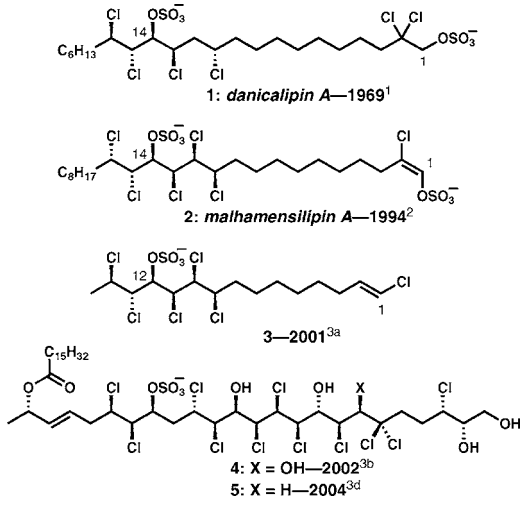
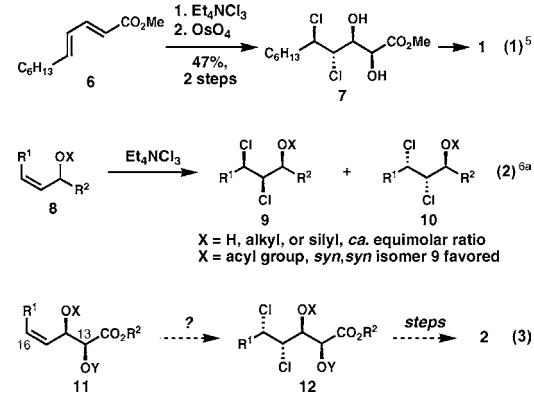


Figure 1. Representative chlorosulfolipids from freshwater algae (**1** and **2**) and from toxic Adriatic mussels (**3**−**5**).

In our work on the stereochemical elucidation of the algae-derived chlorosulfolipids,[2b,5] we were surprised to find that the stereochemistry among lipids **1**, **2**, and **3**, which are presumably derived from similar biosynthetic pathways, is not fully conserved. Initially, we planned to adapt the strategy used in our synthesis of danicalipin A for malhamensilipin A, but we quickly encountered a problem. Whereas in our efforts toward **1**, regioselective and stereospecific dichlorination of the γ,δ-alkene in (*E*,*E*)-diene **6** proceeded smoothly (eq 1), enabling a subsequent diastereoselective dihydroxylation, we were surprised to discover that the dichlorination of the related (*E*,*Z*)-$\alpha,\beta,\gamma,\delta$-unsaturated esters generated equimolar mixtures of diastereomers in a reaction that would prove unsuitable as the foundation of a stereocontrolled synthesis. We also knew from our work on diastereoselective dichlorination of (*Z*)-allylic alcohol derivatives[6a] that the dichlorination of these substrates (**8**; eq 2) tends to be unselective in most cases but can favor the formation of the undesired *syn*,*syn*-dichloroalcohol products when the hydroxyl group is acylated; thus, the possibility of using the stereochemistry of the C14 hydroxyl-bearing stereogenic center to introduce the C15 and C16 chlorides (malhamensilipin A numbering) appeared unlikely (eq 3). Nonetheless, we felt that the opportunity to begin from compounds of type **11**, wherein the diol could be introduced enantioselectively via Sharpless asymmetric dihydroxylation,[9] was worthy of study for the ultimate ability to complete the first enantiocontrolled synthesis of a chlorosulfolipid. We hoped that in some context, the stereogenicity of either C13 or C14 might be relayed in a dichlorination reaction of a C15−C16 alkene. Realization of this strategy was the key to our stereocontrolled synthesis of malhamensilipin A, as described below.



We began our studies with unsaturated ester **13**,[10] which underwent a slow dihydroxylation (>95% ee) under the modified Sharpless dihydroxylation conditions reported by Bittman[11] for a similar enyne ester substrate (Scheme 1). Semireduction of the alkyne using Lindlar's catalyst was unreliable, but P-2 Ni/ethylenediamine cleanly afforded (*Z*)-allylic alcohol **14**.[12] A variety of derivatives of this diol were studied for diastereoselectivity under alkene dichlorination conditions;[13,14] dichlorination of **15**, readily prepared by selective nosylation of the α-hydroxyl group,[5,15] was highly selective (>10:1 dr) for the stereoisomer required for a synthesis of malhamensilipin A. At this time, we do not have a compelling explanation for the selectivity ostensibly

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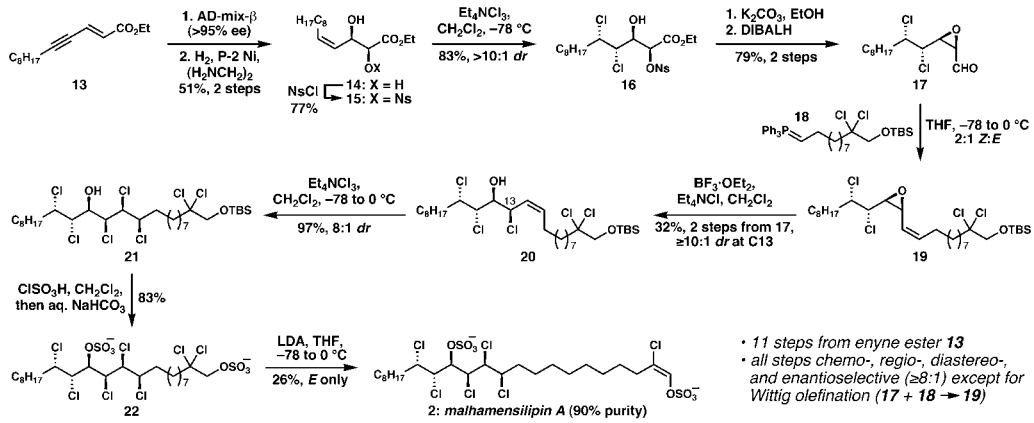
Scheme 1. Synthesis of Malhamensilipin A



imparted to the reaction by the remote nosyl ester; serendipitously, this group was required for the subsequent base-mediated *cis*-epoxide formation (from **16**).[15] Reduction of the ester to the aldehyde (**17**) preceded a Wittig reaction with phosphorane **18**,[5] which proceeded with only modest stereoselectivity (2:1 *Z*/*E*) in the generation of **19**. We had previously developed a chloride-induced vinyl epoxide ring-opening reaction that favors inversion of stereochemistry[5] in the face of potentially complicating participation of the remote chlorides;[4] when applied to the stereoisomeric mixture of Wittig products, this method delivered (*Z*)-allylic chloride **20** in 32% yield from aldehyde **17**. Stereoselective dichlorination of the remaining alkene completed the stereochemical array of malhamensilipin A. The stereocontrol in this step is consistent with that observed by the Carreira group in their synthesis of **1**.[4] At this stage, comparison of the ^{1}H NMR signals attributed to the C11−C16 region of **21** with those from a desulfated derivative of malhamensilipin A[2b] revealed a nearly perfect match with respect to chemical shift and ^{1}H−^{1}H coupling constants, providing strong evidence that we had obtained the natural stereochemical relationships.

To complete the synthesis, introduction of the C14 sulfate and the (*E*)-chlorovinyl sulfate was required. To this end, silyl ether **21** was treated directly with chlorosulfonic acid followed by saturated aqueous $NaHCO_3$ to generate heptachloride bis-sulfate **22**. In a reaction that we had studied in very simple model systems[2b] and that caused us some degree of trepidation, we subjected **22** to an excess of LDA in THF. Examination of the ^{1}H NMR spectrum of the crude reaction mixture revealed the *formation of a single alkene corresponding to malhamensilipin A*; an undesired side product with no alkene was produced in equimolar quantities.[16] In view of the presence of β,β-dichlorinated terminal sulfates in the related lipids of *Ochromonas danica* (see **1**), it is plausible that this reaction has its counterpart in the biosynthesis of **2**. That such a strong base was required to effect elimination suggests that the chlorovinyl sulfate is not an artifact of isolation. Malhamensilipin A (**2**) of ∼90% purity could be isolated in 20−30% yield[17] and exhibited spectroscopic data matching those obtained from a natural sample, thereby confirming the recent structural revision.[2b]

The enantioselective synthesis of malhamensilipin A was completed in 11 steps (longest linear sequence) from known enyne **13** with high stereocontrol in the introduction of all of the polar substituents. The selectivity imposed on the dichlorination of alkene **15** by the remote nosyl ester and the regio- and diastereocontrol of the final elimination reaction are novel aspects of this work; experiments to understand these processes are ongoing and will be described in a more detailed disclosure.

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Supporting Information Available: Experimental details, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Attempts to isolate and characterize this side product were unsuccessful. In view of the lack of alkene-derived signals associated with this product, a C1−C2 alkyne (an alkynyl sulfate) formed via double elimination is a plausible structure. MS analysis of the crude reaction mixture revealed a product with such a mass, but efforts to further characterize it as part of the mixture by ^{13}C NMR and IR did not provide unambiguous evidence in support of this assignment.

(17) Purification via normal- and reversed-phase flash chromatography, HPLC, preparative TLC, extractions, and triturations was attempted; separation of **2** from the starting material and the major side product, both of which also contain two sulfates, proved exceptionally challenging.

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