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Approaches to the Chemical Synthesis of the Chlorosulfolipids

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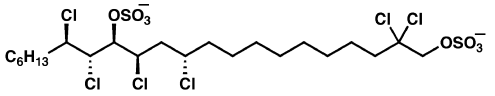
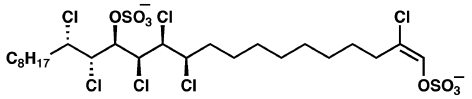
CONSPECTUS

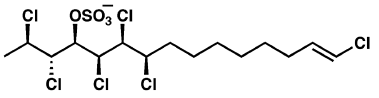
Since the initial discovery of the chlorosulfolipids in 1969, the chemical synthesis community largely ignored these compounds for nearly four decades, perhaps because they contain a high density of chlorine atoms, which suggested that these molecules and any projected synthetic intermediates might be unstable. Beginning in 2008, a sudden flurry of synthesis activity by several research groups, including our own, appeared in the literature. In this Account, we highlight our work from the last several years on the chemical synthesis of the chlorosulfolipids.



danicalipin A
–1st generation synthesis: 13 steps, racemic



malhamensilipin A
–improved 1st generation synthesis: 12 steps, enantioselective



mytilipin A
–2nd generation synthesis: 8 steps, enantioselective
–features Z-selective alkene cross metathesis and kinetic resolution of a complex vinyl epoxide

Our work in this area began with attempts to stereoselectively generate the abundant dichloroalcohol functional group arrangements in these natural targets. In these early studies, we learned that many polychlorinated intermediates were far more stable than anticipated. We also developed a method for the diastereoselective dichlorination of allylic alcohol derivatives that permitted access to the *syn,syn*-dichloroalcohol stereotriad found in several chlorosulfolipids. Concurrently, we investigated an approach to mytilipin A that included multiple intermediates bearing aldehydes with β-leaving groups, but this route proved intractable. However, we leveraged what we had learned from this approach into our first success in this area: we synthesized danicalipin A via a route that introduced all of the polar functional groups using alkene oxidation reactions. By adapting this relatively general strategy, we completed an enantioselective synthesis of malhamensilipin A. This body of work also resulted in the full stereochemical elucidation of danicalipin A and the structural revision of malhamensilipin A.

Finally, with the advent of *Z*-selective alkene cross metathesis, we developed a second-generation synthesis that featured this strategy in place of a poorly performing Wittig olefination that plagued our first approach. In addition to this new convergent step, we developed a reliable protocol for diastereoselective addition to highly sensitive α,β-dichloroaldehydes and a method for kinetic resolution of complex vinyl epoxides. Altogether, these advances led to a synthesis of enantioenriched mytilipin A in only eight steps.

In the context of this work, we discovered a number of highly stereoselective reactions that might offer new, broadly applicable lessons in acyclic stereocontrol. Moreover, this research testifies to the stability of polychlorinated molecules and should inspire confidence in the use of aliphatic chlorides in other applications, including in discovery chemistry.

I. Introduction

Halogenated molecules have attained great prominence in drug discovery, with fluorine as the key player.[1] Fluorine is largely introduced to confer favorable properties to drug candidates, including reducing metabolic liabilities and changing pharmacokinetic profiles. Given the game-changing properties of fluorine in bioactive molecules, it seems reasonable that chlorine might also bestow useful attributes to organic compounds. The concern that alkyl (poly)chlorides are electrophilic and will lead to toxicity issues might be ill-founded. Consider the obvious case of sucralose (Splenda, **1**, Figure 1), the chlorinated sucrose derivative used extensively as a non-nutritive sweetener. Apparently, alkylation of biomolecules by either the primary or secondary chloride-bearing electrophilic carbons is not facile, at least not with a high local concentration of inductively electron-withdrawing groups. In short, it is not unreasonable to suggest that the judicious use of chlorine

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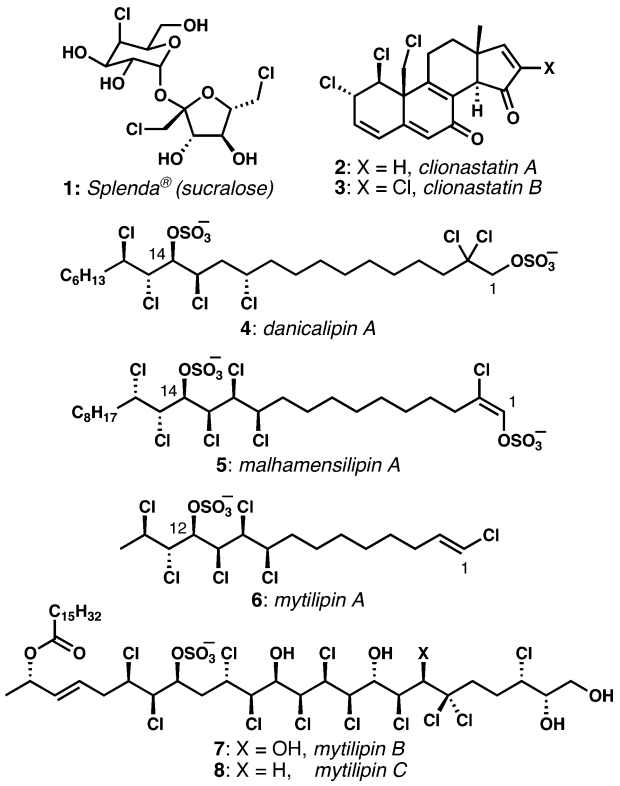


FIGURE 1. Structures of Splenda, the clionastatins, and several chlorosulfolipids.

bound to sp^3-carbon might be significant in drug discovery. In this Account, we discuss our research group's interest in polychlorinated natural products, with a focus on chlorosulfolipid synthesis, from which we have learned that alkyl chlorides are often surprisingly stable and well-behaved and that they do impart interesting properties to organic molecules.

The corresponding author's interest in chlorinated molecules began during postdoctoral studies (Harvard University, Jacobsen group), when the clionastatins (**2** and **3**) were reported by the Fattorusso group,[2] coincidentally the same group who discovered the mytilipins, a small family of chlorosulfolipids (see below). The clionastatins are highly unusual androstane steroids; they are certainly the most chlorinated steroids currently known, but they are also peculiar with respect to their unusual oxidation pattern. When we considered the clionastatins as targets, several questions arose, including: (1) Would the chlorides be simple to introduce in a stereocontrolled manner? (2) Would they be too reactive to carry through multistep sequences? In thinking about the challenges that the high local concentration of chlorine atoms posed, we recognized the opportunities presented by polychlorinated natural products in general. We initially directed our efforts toward the chlorosulfolipids,[3] rather than the clionastatins, because of the prospect of focusing largely on the characteristics of polychlorides, without the concerns of other challenging architectural elements.

The chlorosulfolipids were first encountered independently by the groups of Vagelos and Haines in the late 1960s, who were studying the biochemistry of the alga *Ochromonas danica*.[4] Their combined studies culminated in the identification of a series of 22-carbon lipids, each with two sulfates and with a range of zero to six chlorines, the most chlorinated of which is now known as danicalipin A (**4**, Figure 1). Clever chemical and mass spectrometric experiments led to structural assignments that persist today,[4] although the stereochemical details that could be elucidated with the methods available at the time were few. These chlorosulfolipids are major components of the cell and flagellar membranes of *O. danica*; however, on account of their two distal polar groups and single chains, it is difficult to fathom how these chlorosulfolipids might engage in membrane bilayer formation.[3a]

Much later, malhamensilipin A (**5**), a moderate inhibitor of protein tyrosine kinase, was isolated from the related alga *Poterioochromonas malhamensis* by the groups of Gerwick and Slate.[5] The relative and absolute configurations could not be assigned with the methods available at the time. The unusual chlorovinyl sulfate likely arises from biosynthetic elimination from a dichloro sulfate of the type seen in danicalipin A. Finally, in a series of papers since 2001,[6] the Fattorusso group reported three new chlorosulfolipids isolated from toxic mussels harvested from the Adriatic Sea. Originally unnamed, these compounds were recently named mytilipins A, B, and C (**6**, **7**, and **8**), owing to their provenance from the species *Mytilus galloprovincialis*. Although obtained from mussels, it is likely that these chlorosulfolipids are also algal products that are bioaccumulated in higher organisms; recent support for this idea comes from the isolation of mytilipin A and analogues from an octocoral taken from the Strait of Taiwan.[7]

In the spring of 2006, when we initiated our chlorosulfolipid work, it had been roughly 37 years since the first report of the existence of chlorosulfolipids,[4a,b] and the only synthesis work in this area was aimed at structure determination of some of the simpler, least chlorinated members isolated from *O. danica*.[4b,c] Some biochemical and biosynthetic studies were published in the decade following their discovery.[3a] Otherwise, research into the chlorosulfolipids appeared to be largely at a standstill, and we thought (incorrectly) that this neglected and obscure yet fascinating area of natural products chemistry had been left to us to

study. We eagerly embarked on a program to learn about the stereocontrolled synthesis, reactivity, and physical properties of polychlorinated alkanes, with the laboratory syntheses of many of these natural products as our midrange goals. Greater understanding of the roles of chlorosulfolipids in the producing organisms, their biological properties, and their biosynthesis were and remain long-term objectives of this program.

II. First Approaches Based on Carbonyl Additions and Diastereoselective Dichlorination of Allylic Alcohols

At the outset of our work, we recognized that the synthesis of the chlorosulfolipids might benefit from methodologies involving chloroacetate aldol additions to halogenated aldehydes (and related allylation reactions), as well as diastereocontrolled dichlorination of allylic alcohols. In other words, our first foray into chlorosulfolipid synthesis would combine aldol-like chemistry (with the view that these targets at least somewhat resemble polyketides) with stereoselective alkene chlorination reactions. Because the all-vicinal dichloroalcohol motif was present in all four diastereomeric forms among the mytilipins (the only chlorosulfolipids of known configuration at the beginning of our studies), we aimed to define routes to each stereoisomer. With flexibility in principle deriving from the ability to choose either *E*- or *Z*-allylic alcohol starting materials, as well as *syn*- or *anti*-dichlorinating reagents, and the possibility of hydroxyl direction to or steric direction away from diastereotopic alkene faces, we thought that this would be a manageable project (Figure 2).

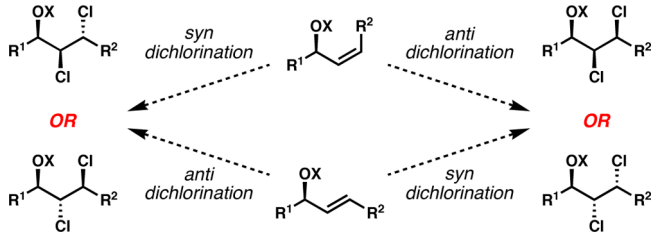
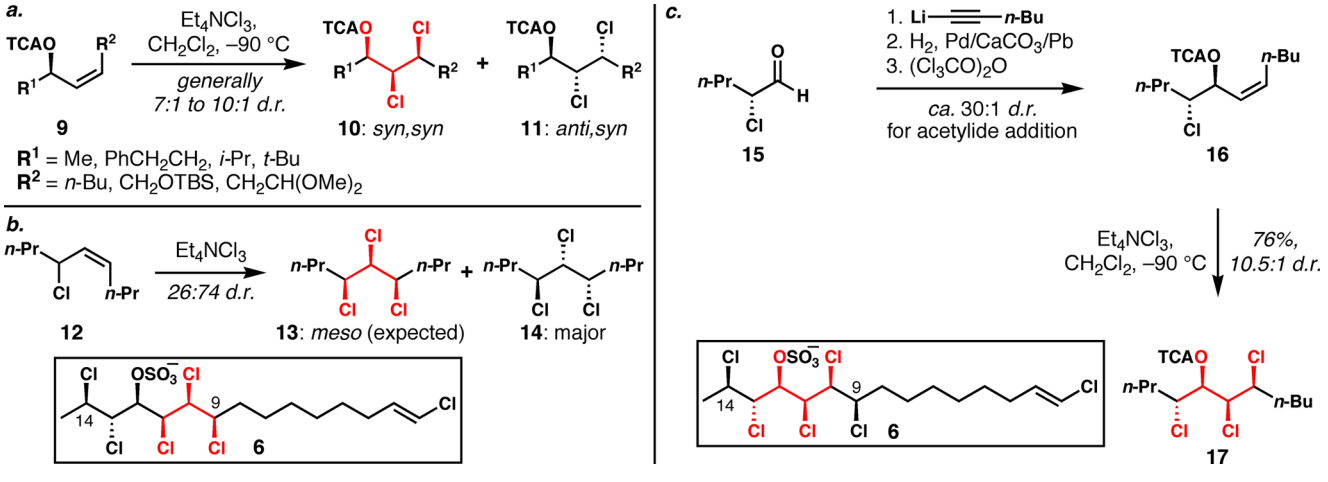


FIGURE 2. Possible access to all diastereomeric products.

After extensive surveys of the reactivity of *syn*- and *anti*-dichlorinating agents toward *E*- and *Z*-allylic alcohols and derivatives, we found that we could cleanly access the *syn,syn*-dichloride (**10**) via dichlorination of *Z*-allylic trichloroacetates **9** (Scheme 1a) with Et_4NCl_3 (Mioskowski's reagent).[8] Unfortunately, efforts to access the other diastereomers were unsuccessful. Based on the naïve idea that allylic trichloroacetates and allylic chlorides would behave similarly, we were surprised to find that *Z*-allylic chloride **12** afforded the *anti,syn*-diastereomer **14** in preference to the expected product **13** (Scheme 1b). This result clearly demonstrated that we had little understanding of the rules governing stereoselectivity. Indeed, the allylic trichloroacetate context would be the first of many times that we observed high selectivity in the chlorosulfolipid project that was not easily rationalized. We next increased the complexity of our starting materials and made allylic chlorohydrin **16** from α-chloroaldehyde **15** as shown (Scheme 1c). Chlorination was still highly selective in this more complex context, affording a stereotetrad (**17**) corresponding to C10–C13 of mytilipin A (**6**) with high diastereoselectivity.[8] However, this overall approach was not likely to be fruitful for mytilipin A, because we would need a strategy that incorporates the chlorides at C9 and C14 (those flanking the stereotetrad found in **17**), and we were unable to conceive of an attractive way to do so.

SCHEME 1. (a) Diastereoselective Dichlorination of *Z*-Allylic Trichloroacetates, (b) Unexpected Selectivity in the Dichlorination of *Z*-Allylic Chlorides, and (c) Extension to the Stereotetrad of Mytilipin A

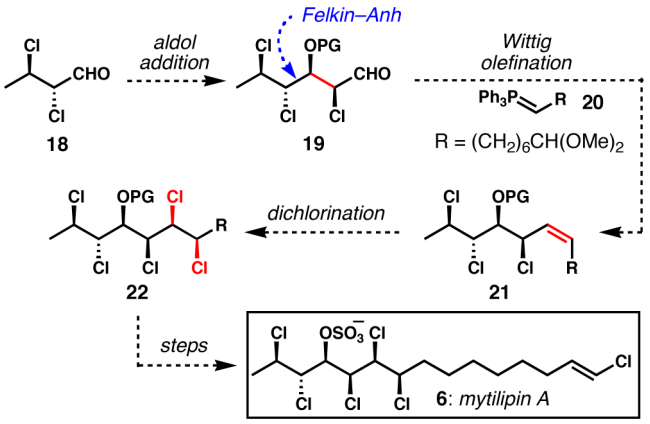


At this point, we had attained a level of comfort with polychlorinated compounds, and we decided to simultaneously target mytilipin A and the major chlorosulfolipid from *O. danica* (danicalipin A, **4**, Figure 1), because we had reason to suspect that their relative configurations would be identical, at least throughout the left-hand stereotetrad. This supposition was based on three different points: (1) their biosynthesis seemed likely to be closely conserved; (2) in early studies,[4b,9] Haines had put forth the C13–C14 and C14–C15 stereorelationships in partially chlorinated lipids (that are likely biosynthetic precursors to danicalipin A), and they matched the corresponding ones in mytilipin A; (3) the reported ^3J couplings along that stretch of each chlorosulfolipid were virtually identical.[5,6a,10,11] To help confirm this hypothesis, we contacted Prof. Thomas Haines, one of the early discoverers of the *O. danica* chlorosulfolipids. He graciously provided a sample of desulfated danicalipin A. This sample had been isolated, desulfated, and partially purified at least 25 years earlier and had been stored neat on the benchtop in a simple stoppered vial, with no protection from moisture, light, or air. Upon inspection, we found it to be in exactly the condition that Prof. Haines had described, and we used it for stereochemical determination and as an authentic sample. Coupled with the lack of degradation of most of our samples of dichlorination products of type **10**, this observation made it clear to us that vicinally polychlorinated molecules are generally very stable compounds. This conclusion heartened us when proposing the isolation and storage of compounds that would normally be unstable, such as allylic chlorides.

One of the early approaches that we envisioned and investigated for mytilipin A (with slight variations toward danicalipin A) is shown in Scheme 2. Diastereoselective nucleophilic addition to α,β-dichloroaldehydes and the diastereocontrolled dichlorination of a complex allylic chloride were two of the key projected steps. In addition to these questionable plans, another specific liability in this approach was the necessity of performing a convergent Wittig olefination on an α-chloro-β-alkoxy-aldehyde. We spent the better part of a year on this plan, but the poor behavior of the dichloroaldehyde starting materials and the ineffective Wittig olefinations of the small quantities of aldehydes of type **19** that we could access led us to change tactics.

A comment about the proposed dichlorination of complex *Z*-allylic chloride **21** is warranted. As shown above in Scheme 1b, simple *Z*-allylic chlorides were dichlorinated with poor diastereoselectivity, favoring the undesired *anti*, *syn* products. For our synthesis to be successful, we required

SCHEME 2. Aldol/Wittig Strategy To Access Key Dichlorination Substrate **21**



the opposite stereochemical outcome. Our careful consideration of the preferred solution conformation of the natural product itself (Figure 3)[6a] led us to the proposition that complex substrate **21** might behave the way we desired, owing to increased diastereoface selectivity resulting from projection of a bulky oxygen protecting group over the back face. This thought also turned out to be self-serving, in providing us the necessary inspiration to go forward.

III. Our First Successful General Approach to the Chlorosulfolipids: Danicalipin A

We assumed that targeting mytilipin A, with its known configuration, would set the stage for syntheses of danicalipin A and malhamensilipin A, with attendant confirmation of the hypothesis that their configurations would match that of mytilipin A (Figure 4a). At this time, we were having problems elucidating the relative and absolute configuration of

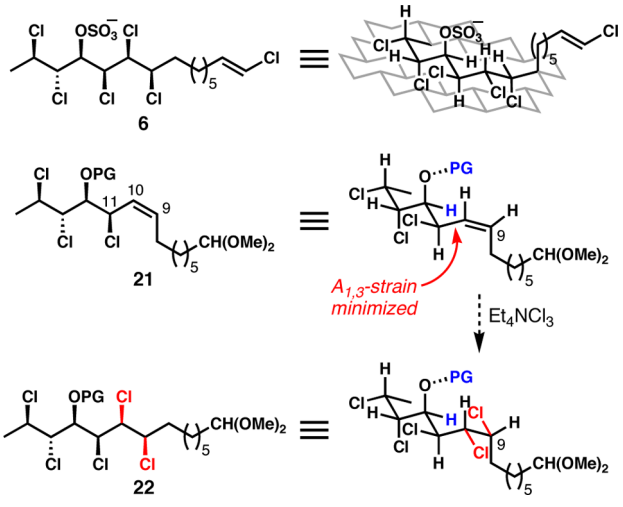


FIGURE 3. Solution conformation of mytilipin A and the possible conformationally controlled dichlorination.

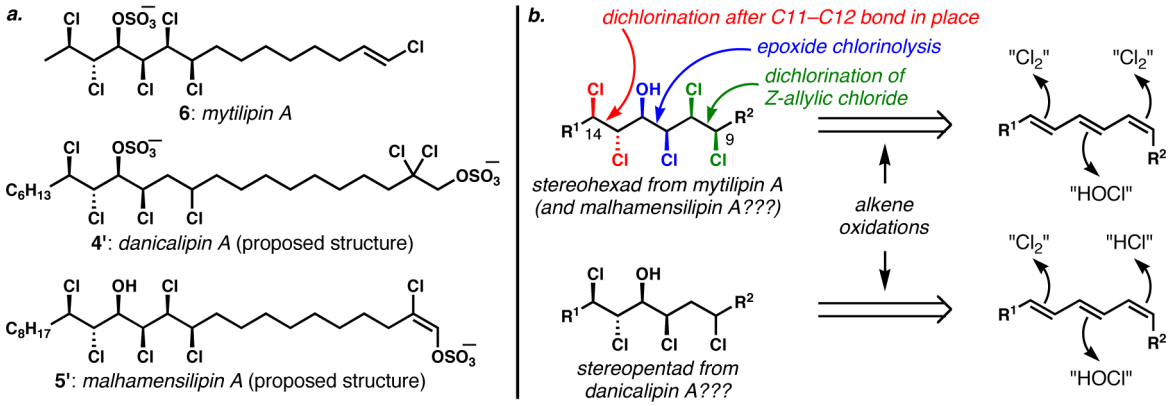


FIGURE 4. (a) Initially presumed stereochemistry of danicalipin A and malhamensilipin A based on analogy to mytilipin A. (b) Alkene oxidation strategy to access these three chlorosulfolipids.

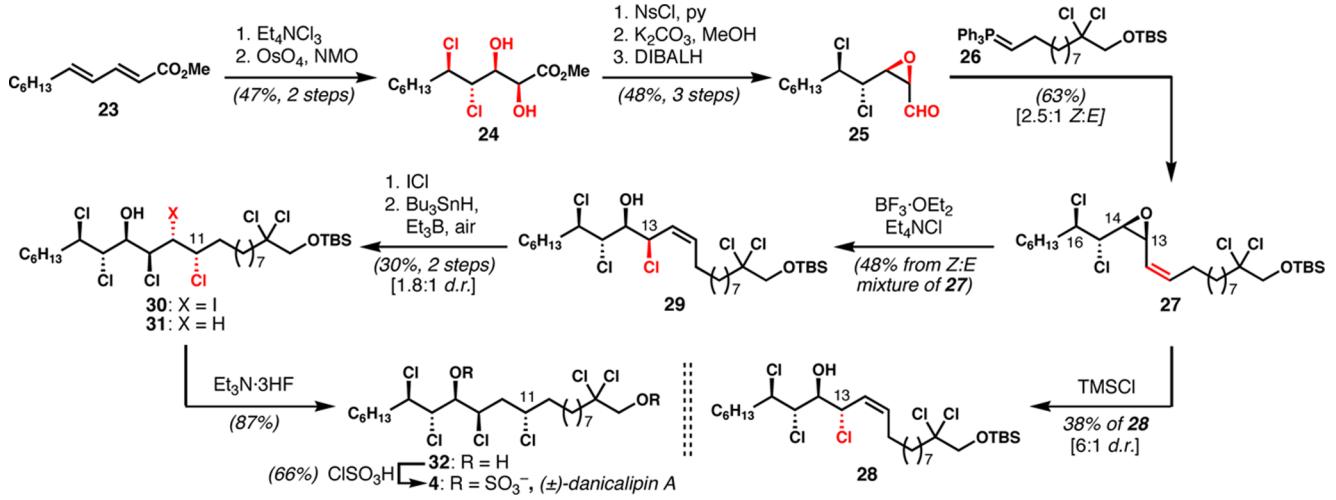
danicalipin A using the natural sample provided by Prof. Haines. The Murata JBCA method[12,13] that had been adapted by Fattorusso et al. for the structural elucidation of the mytilipins proved difficult to implement. With no sample of malhamensilipin A, it seemed that the best way to decipher the configurations of these two algal-derived lipids would be by synthesis in parallel with our mytilipin A work, which we began in earnest with a new approach.

One of the hallmarks of our early thinking was that most of the chlorine substituents would be introduced by alkene oxidation reactions, which must be about the most efficient way to deal with these targets. The major liabilities of our first approach centered around the marked instability of α,β-dichloroaldehydes in attempted nucleophilic addition reactions as well as the poor behavior of aldehydes with β-leaving groups toward Wittig olefinations. We surmised that we could avoid the instability of the dichloroaldehydes entirely by delaying the introduction of the C13/C14 chloride residues (mytilipin A numbering), perhaps until the C11–C12 bond was in place. We thought that we might retain the convergent Wittig reaction that forges the C9–C10 bond if we used an α,β-epoxyaldehyde as a surrogate for the chlorohydrin that had been so poorly behaved. This idea presented the opportunity to introduce *all* of the polar substituents by alkene oxidation reactions on hypothetical triene precursors of the type shown in Figure 4b.

On the basis of our "triene functionalization strategy", we began with commercially available ethyl sorbate and worked toward mytilipin A. We had made significant progress in this regard (not shown, owing to the parallel chemistry shown toward danicalipin A below), when we were surprised by the Carreira group's mytilipin A synthesis.[14] Having thought that we were all alone in this unusual corner of natural product synthesis, this turn of events came as a shock. Normally being a close second in complex natural product synthesis would be of only minor concern; however, the great similarity of Carreira's approach to ours required a readjustment to a new chlorosulfolipid target; with an authentic sample of danicalipin A in hand, we quickly focused our efforts exclusively on this target to maintain our footing in what had suddenly become a competitive area. While malhamensilipin A might look like an easier translation from mytilipin A, we were rather concerned about the introduction of the unprecedented chlorovinyl sulfate.

Starting from known dienoate (triene surrogate) **23** (Scheme 3), dichlorination of the less electron-poor alkene preceded diastereoselective dihydroxylation of the remaining alkene. Simple functional group manipulations converted the dichlorodiol ester **24** to epoxyaldehyde **25**, the substrate for a convergent Wittig reaction. This key step proved troublesome and poorly reproducible, at best a 60–65% yield of a 2.5:1 *Z*/*E* mixture of product **27**. Nonetheless, all of the carbon atoms of the target were assembled, the C15 and C16 chlorine-bearing stereogenic centers were installed, the C14 carbon–oxygen bond was correctly configured, and the C13 allylic terminus of the epoxide was activated for ring-opening chlorinolysis. That would leave the alkene as a means to bring in the final chloride of the target (in our efforts toward mytilipin A, a dichlorination of that alkene would be required, and of course, the left-hand and right-hand chains would be different). When we used Llebaria's protocol[15] for vinyl epoxide chlorinolysis on some painstakingly purified **27**, we were surprised to obtain a mixture of diastereomeric chlorohydrins. Still without routine access to *J*-based configurational analyses, we took the two diastereomers and independently converted them back to vinyl epoxides under basic conditions (we resorted to this tactic frequently in the

SCHEME 3. Our First Generation Synthesis of Danicalipin A



early days of our work[8]), thus learning that opening had occurred predominantly with retention of configuration at C13, yielding **28**. It was while we were learning this lesson in the context of mytilipin A (same chemistry as **23** to **28**, just starting with ethyl sorbate and using a different Wittig phosphorane) that we were shocked by Carreira's synthesis of mytilipin A,[14] complete with the same unusual stereochemical result that we had just happened upon and an explanation based on chlorine participation. Clearly, these chloride residues cannot be viewed as innocent bystanders in all cases and are capable of anchimeric assistance. As a result, stereochemical outcomes of reactions in these contexts must be rigorously determined.

Carreira's solution to the unexpected stereochemical outcome was to rework his synthesis from the beginning to introduce in a *trans*-epoxide, such that the stereoretentive ring-opening chlorinolysis gave the desired diastereomeric product. Because it was a simpler solution, and to avoid being derivative, we opted to define chlorinolysis conditions under which the *cis*-epoxide underwent opening with inversion of configuration. Fortunately, we quickly found that an excess of soluble chloride with boron trifluoride etherate effected a reasonably efficient ring-opening of **27** from which only the desired diastereomer **29** was observed and isolated. Fortuitously, when the isomeric mixture of alkene Wittig products (which were very difficult to separate) was subjected to these conditions, the *E*-isomer underwent apparent decomposition, and the desired *Z*-allylic chloride was obtained cleanly from the reaction mixture. Material throughput was not severely hampered by the low-yielding two-step sequence, and hundreds of milligrams of allylic chloride **29** were obtained.

Introduction of the "isolated" C11 chloride was best accomplished via iodochlorination/deiodination. Iodochlorination gave **30** (ca. 1.8:1 dr, but complete regiocontrol), and tributyltin hydride reduction when initiated with triethylborane/air at −78 °C afforded **31** efficiently. Separation of the resulting diastereomers proved challenging because they differed only with respect to the configuration at the somewhat remote C11-chlorine-bearing stereogenic center, but significant quantities of pure **31** could be obtained by PTLC.

When hexachloride **31** was desilylated, we were ecstatic to see that it was a spectroscopic match for the sample obtained from Haines. Sulfation with chlorosulfonic acid to initially generate the bis(sulfonic acid) followed by treatment with aqueous sodium bicarbonate generated racemic danicalipin A, presumably as the disodium salt.[16] While the synthesis of this chlorosulfolipid was complete, curiously, we were still unaware of its relative configuration, owing to our problems implementing the JBCA method.

At about this time, we began a fruitful collaboration with the Gerwick group at UCSD. This group had been involved in the isolation of malhamensilipin A 15 years prior and were experts in the NMR methods that facilitated JBCA. We quickly learned that the relative configuration of the natural product was as shown in Scheme 3, which was somewhat surprising because the C11-chlorine-bearing center was opposite to that found in mytilipin A. Although our synthesis produced racemic material, we used the enantiopure natural sample from Haines to determine the absolute configuration of danicalipin A using the modified Mosher ester analysis. It was satisfying to find that it fell into the same enantiomeric series as mytilipin A. We were ultimately able to submit our work for publication[16] less than two months after the first

synthesis of mytilipin A was published by the Carreira group. Contemporaneously with our efforts that culminated in the establishment of the relative and absolute configuration of danicalipin A, the Okino group isolated eight chlorosulfolipids in a reinvestigation of *O. danica*, with the purpose of determining their configurations.[11] Pleasingly, all of the data were consistent.

IV. Structure Determination and Enantioselective Synthesis of Malhamensilipin A

With the structure of mytilipin A confirmed by Carreira's synthesis and the series of danicalipins fully characterized, malhamensilipin A was the only remaining structural question. Its two-dimensionsal structure was proposed by the Gerwick and Slate collaboration in 1994,[5] prior to the establishment of the JBCA method, so its configuration was unknown. Structure **5′** in Figure 5 is that originally put forth by Gerwick and Slate, with the configuration from mytilipin A superimposed; this structure, with or without a C14 sulfate, was the one we considered likely. Still, we embarked on a reisolation/structural elucidation campaign prior to our synthesis efforts because there was clear risk involved in blindly targeting **5′** given the differences already seen between danicalipin A and mytilipin A. With the Gerwick group, we completed a structural revision of malhamensilipin A that provided its absolute and relative configurations, confirmed the *E*-configuration of the chlorovinyl sulfate, and corrected the structure to a bis(sulfate) (**5** in Figure 5).[17] The configurations at C11 and C16 differ from danicalipin A, and that at C16 differs from mytilipin A. In short, all three of these chlorosulfolipids are stereochemically distinct, although all fit into the same stereochemical series (using the secondary sulfate as the point of reference).

The first attempts to elucidate the relative configuration of malhamensilipin A by JBCA led to ambiguous results. Key NOE correlations to distinguish between the two configurations **5** and **5″** could not be obtained on the natural product itself. In our bid to remain competitive in an area of increased activity, our synthesis efforts thus proceeded

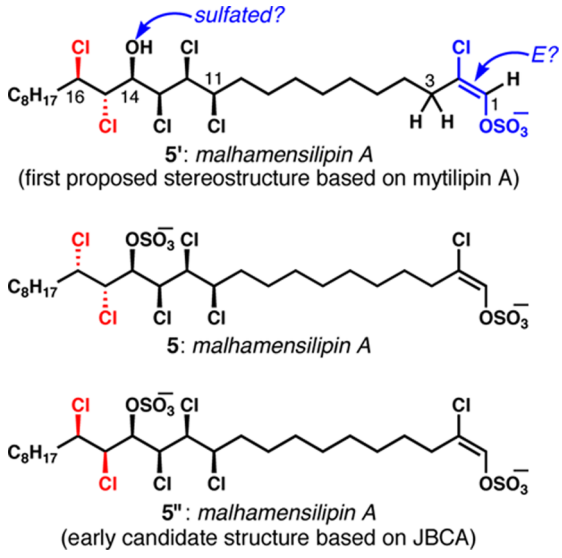
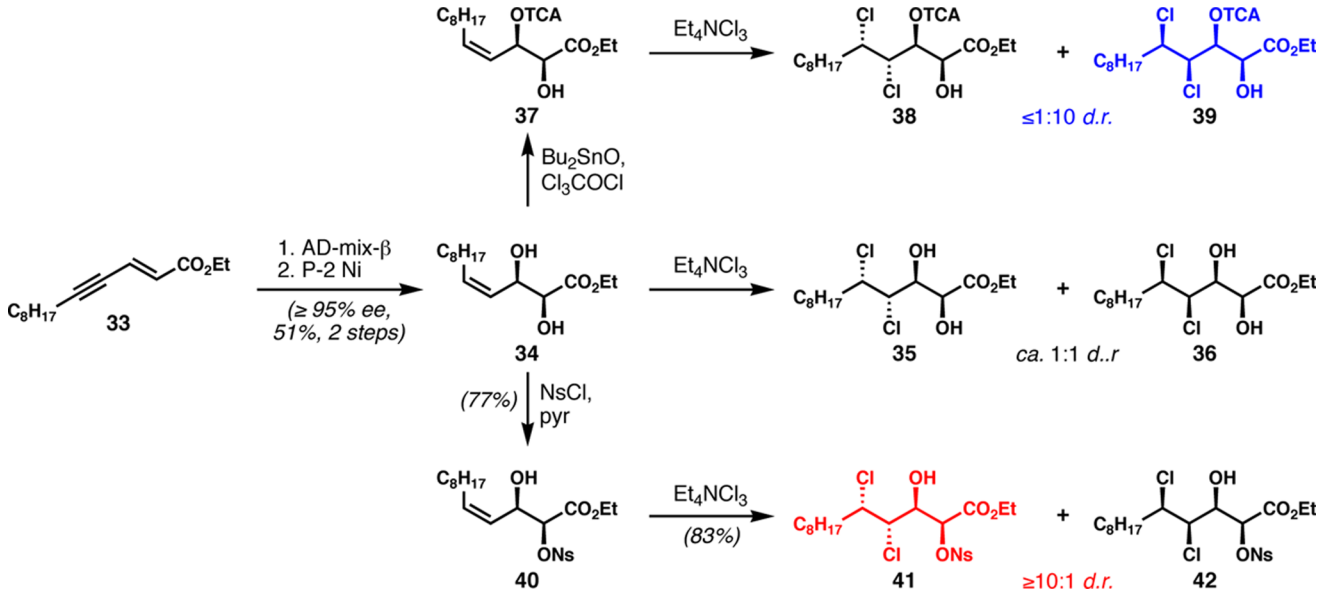
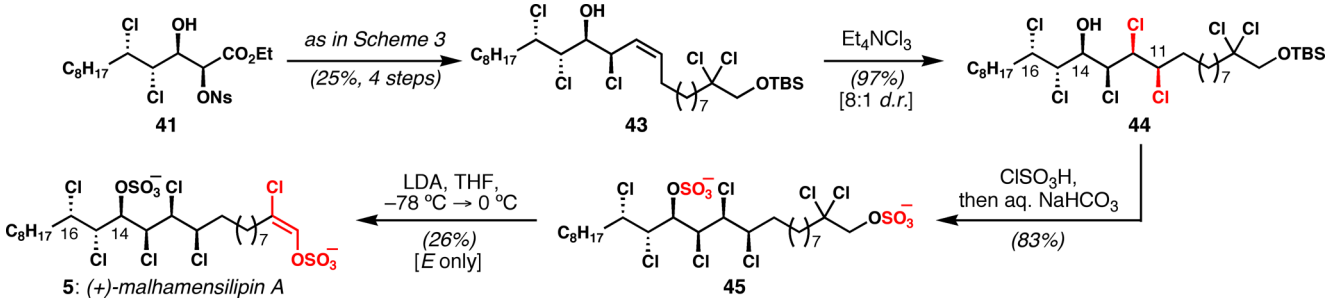


FIGURE 5. Candidate structures of malhamensilipin A.

SCHEME 4. Divergent Dichlorination Outcomes of Allylic Diol Derivatives



SCHEME 5. Completion of the Enantioselective Synthesis of (+)-Malhamensilipin A



along two distinct but parallel lines aimed at these two diastereomeric targets. These two investigations diverged from a key intermediate, which allowed us to pose a fascinating question: from an intermediate of type **34** (Scheme 4), could we access either the *syn,anti,syn* (**35**) or the all-*syn* (**36**) stereotetrad by diastereocontrolled alkene dichlorination? This idea was attractive because **34** could be prepared by Sharpless asymmetric dihydroxylation of enyne ester **33** followed by alkyne semireduction; an enantioselective synthesis was therefore reasonable. We predicted that the all-*syn* product would be formed by dichlorination of the allylic trichloroacetate,[8] if we could find a simple way to chemoselectively monoacylate the diol. On the other hand, we had no idea of how to gain access to the other diastereomer.

To establish a baseline, we treated enantioenriched **34** with Et_4NCl_3 and obtained an equimolar mixture of diastereomeric dichlorides **35** and **36**, consistent with our previous results with simpler *Z*-allylic alcohols.[8] Tin oxide acetal methodology facilitated selective trichloroacetylation of the allylic hydroxy group. Dichlorination of **37** provided the all-*syn* diastereomer **39** as the major component of a 10:1 diastereomeric mixture.

Selective nosylation of the hydroxy group α to the ester, a transformation that would later permit epoxide formation (see **24** → **25**, Scheme 3) afforded **40** in high yield. Dichlorination of this compound proceeded with complete diastereoselectivity; surprisingly, the product turned out to be *syn*, *anti,syn* diastereomer **41**! To date, we do not understand the underlying reasons for the complete reversal of diastereoselectivity between **37** and **40**.

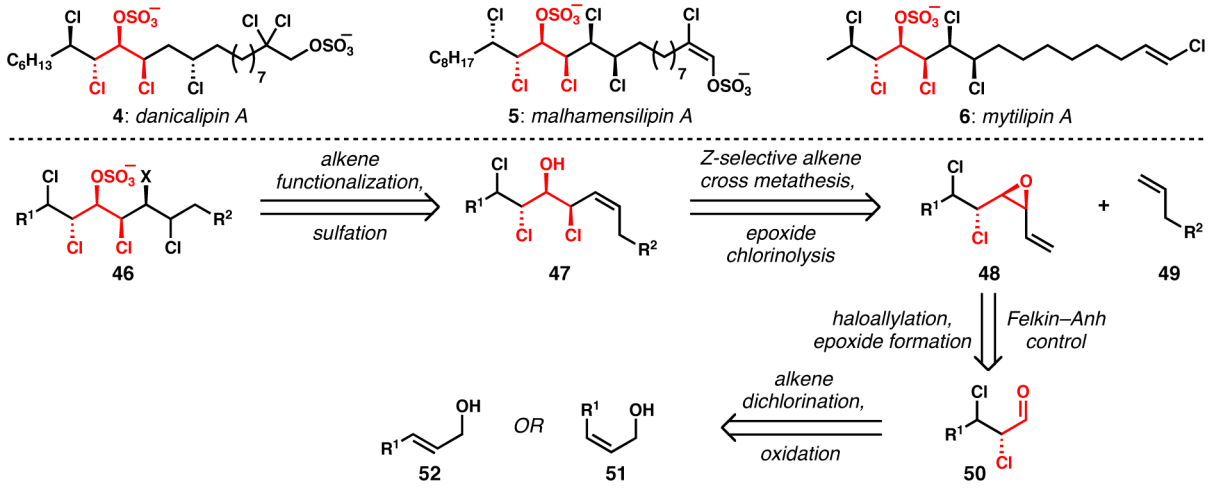
Sulfonate ester **41** was converted into *Z*-allylic chloride **43** using the identical four-step sequence used for danicalipin A. (Schemes 3 and 5). Dichlorination of **43** yielded stereohexad **44**, which displayed nearly identical C11–C16 methine resonances as the desulfated chlorosulfolipid target. Here, as we had hoped and as Carreira had observed in the context of mytilipin A,[14] the dichlorination was highly *syn*-selective, in contrast to the simple model shown in Scheme 1b. All of the *J*-based configurational analyses for synthetic compound **44** and the newly isolated natural product came together at roughly the same time and permitted us to disclose the structural revision of malhamensilipin A as we sorted out the final details of the synthesis;[17] clearly, the stereocontrolled introduction of the daunting chlorovinyl sulfate was looming.

We found that we could directly introduce both the C1 and C14 sulfates using chlorosulfonic acid, without the need to remove the C1-silyl ether of **44** in a separate prior step. For several reasons, our best plan to install the chlorovinyl sulfate involved a chemo- and stereocontrolled elimination of a single equivalent of HCl from this precursor that has seven chlorides and two sulfates: (1) it likely paralleled its biogenesis; (2) it allowed the use of the same Wittig phosphorane and similar end-game to our danicalipin work; (3) we had accomplished such an elimination in a model system used for the stereochemical determination work; (4) we did not have any better ideas, having previously failed to convert α-chloroaldehydes and α,α-dichloroaldehydes to the desired functional group via enolization and *O*-sulfonation. As we had found in model systems, this elimination is not so facile, and an excess of LDA was required to effect conversion. The reaction outcome was as good as we could have hoped: the C11–C16 portion of the molecule was completely untouched, and only the β,β-dichlorosulfate was operated upon, yielding malhamensilipin A in about 20–30% yield over the two steps; the low yield was at least partially attributable to difficulties in purification. This accomplishment[18] and the contemporaneous synthesis of mytilipin A by the Yoshimitsu group[19] constitute the first enantioselective syntheses of chlorosulfolipids.

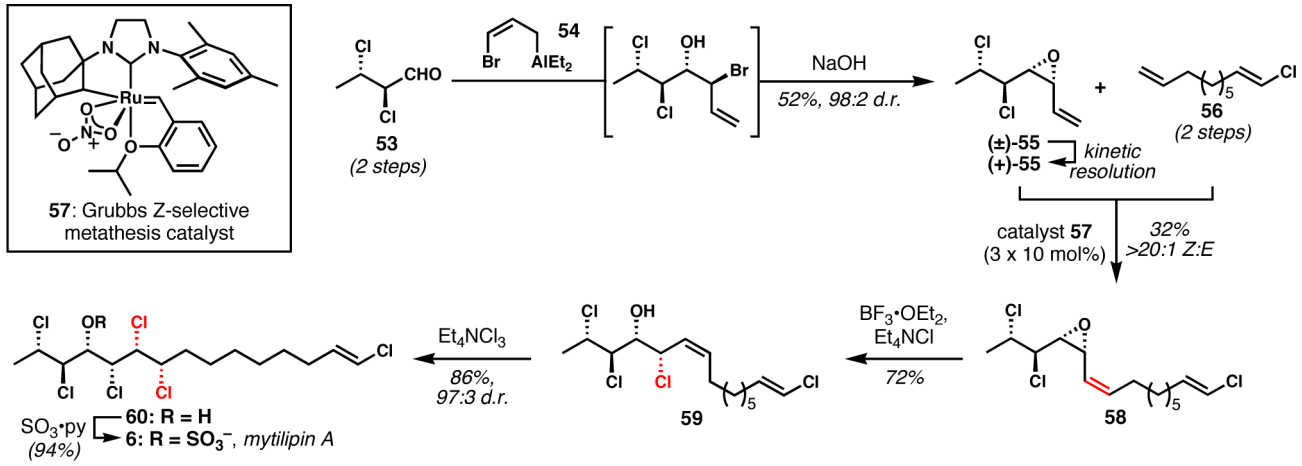
V. A Second-Generation Approach Results in a Short Synthesis of Mytilipin A

As pleased as we were with the outcomes of our synthesis campaigns toward danicalipin A and malhamensilipin A, there were liabilities in each accomplishment. Both suffered

SCHEME 6. Second General Approach to Danicalipin A, Malhamensilipin A, and Mytilipin A



SCHEME 7. Short Synthesis of Mytilipin A



from the unreliable convergent Wittig reaction, and the danicalipin A synthesis had several critical issues of stereocontrol, in addition to producing racemic material. We had long hoped to revisit a carbonyl addition strategy to these chlorosulfolipids, specifically in combination with a replacement of the Wittig reaction by a *Z*-selective alkene cross metathesis reaction (Scheme 6). If feasible, we envisioned syntheses of each of the three chlorosulfolipid targets via sequences of ten steps or less. At the time of conception of this idea, *Z*-selective cross metathesis was in its infancy;[20] furthermore, additions to α,β-dichloroaldehydes remained problematic, and we had no initial idea how to render our syntheses enantioselective. Fortunately, over several years of effort, these problems were eventually resolved.

After much exploration, we found that this approach really shines with mytilipin A (Scheme 7). α,β-Dichloroaldehyde **53** was prepared by dichlorination of crotyl alcohol and oxidation. We found that reactions that presumably proceed via closed transitions states perform well with these types of sensitive aldehydes; for example, a highly diastereoselective bromoallylation/epoxide formation afforded **(±)-55**, which could be resolved by adapting Denmark's desymmetrizing ring-opening chlorinolysis of *meso*-epoxides (not shown).[21] Although convergent cross metathesis required high loadings of the Grubbs catalyst **57**[22] and proceeded only in low yield, it was completely *Z*-selective, and racemic vinyl epoxide **58** was available in significant quantities in only four steps from crotyl alcohol. A key advance was the direct incorporation of the vinyl chloride, which was built in at the end of previous syntheses.[14,19] Completion of the synthesis required only epoxide chlorinolysis, chemo- and diastereoselective dichlorination of the allylic chloride

(in the presence of the vinyl chloride), and sulfation. Ultimately, this new approach yielded racemic mytilipin A in only seven steps and nearly 9% overall yield; enantioenriched chlorosulfolipid can be accessed in only eight steps.[23] This new route featured the productive use of a sensitive α,β-dichloroaldehyde electrophile and provided further evidence for the ever-expanding reach of metathesis processes in complex molecule synthesis.

VI. Conclusions and Outlook

In the course of our chlorosulfolipid work, we have learned much about the reactivity and stability of polychlorinated molecules, accidentally uncovered numerous examples of unexpectedly high levels of stereocontrol, and developed two reasonably general approaches to the small group of related targets danicalipin A, malhamensilipin A, and mytilipin A. In conjunction with the excellent work of others,[6a,11,14] we have learned that these three compounds and related less chlorinated lipids all share the same configuration at the secondary sulfate-bearing stereogenic center, the common point of reference among these compounds. However, many fascinating questions remain.[24]

Going forward, we feel that the following are worthy of study: (1) the generality and underlying mechanisms of the many dramatic instances of acyclic stereocontrol; (2) the rules for halogen participation via cyclic halonium ions and development of useful reactions based on this reactivity; (3) the biosynthetic chlorination processes, including the mechanism and enzymology of C−H chlorination and the molecular recognition involved in selectivity; (4) the biological roles of the chlorosulfolipids. In addition, at least one glaring hole in our synthesis abilities remains: despite some recent fascinating advances,[25] there is not yet a general and reliable method for asymmetric dichlorination of alkenes of any type.

In closing, it is fair to say that polychlorinated molecules need not be feared for their high reactivity; rather, chlorine's inductive electron-withdrawing ability imbues stability on functional group arrangements that in other contexts can prove very reactive. In the cases of alkanes with multiple vicinal chlorines, the polar atoms confer preferred low energy conformations in most cases, permitting predictable control of molecular shape in solution. These aspects of polychlorinated molecules, coupled with the ease of chlorine introduction, offer the possibility of real utility in the molecular design of bioactive molecules, as a complement to their fluorinated counterparts.

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BIOGRAPHICAL INFORMATION

Won-jin Chung was born in Won-ju, South Korea, in 1979. He obtained a B.S. degree in Chemistry from Korea Advanced Institute of Science and Technology in 2002 and a Ph.D. degree from University of Illinois at Urbana−Champaign under the direction of Prof. Scott Denmark in 2008. After completion of Korean military service in 2011, he began postdoctoral studies with Prof. Christopher Vanderwal at the University of California, Irvine.

Chris Vanderwal was born in Germany in 1973, but raised in Canada. He received B.Sc. (Biochemistry, 1995) and M.Sc. (Chemistry, 1998) degrees from the University of Ottawa. He earned his Ph.D. (2003) with Prof. Erik Sorensen at the Scripps Research Institute. After postdoctoral work with Prof. Eric Jacobsen at Harvard, Chris joined UC Irvine in 2005, where he is currently Professor of Chemistry. His group focuses on complex molecule synthesis, targeting polychlorinated natural products, alkaloids, and terpenes.

FOOTNOTES

The authors declare no competing financial interest.

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