Natural Product Synthesis

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A Synthesis of the Chlorosulfolipid Mytilipin A via a Longest Linear Sequence of Seven Steps**

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Dedicated to Professor Larry Overman on the occasion of his 70th birthday

The chlorosulfolipids are a most unusual group of lipids, known since the independent reports of chlorinated C_{22} lipids isolated from the alga *Ochromonas danica* by the groups of Vagelos and Haines in 1969.[1,2] These first compounds were characterized as bis-sulfates of 1,14-docosanediol, with varying levels of chlorination up to the hexachloride, now known as danicalipin A (**1**; Figure 1). In the decades since, this family has grown to include ill-characterized C_{24} analogues (also from *O. danica*),[3] the unusual chlorovinyl sulfate-containing lipid malhamensilipin A (**2**) that was isolated from the related alga *Poterioochromonas malhamensis* by Slate and Gerwick,[4] and the mytilipins, a small group of lipids isolated in very small quantities from toxic Adriatic mussels and reported by Fattorusso and co-workers.[5,6] These last compounds include the C_{15} lipid mytilipin A (**3**), which has some structural resemblance to danicalipin A and malhamensilipin A, and mytilipins B and C (**4** and **5**), two C_{24} lipids with an astounding level of stereochemical complexity that includes 11 chlorine-bearing centers. More recently, Okino and co-workers uncovered more natural congeners in the danicalipin series in a careful study of *O. danica*,[7] and Sheu and co-workers isolated analogues of mytilipin A from an octocoral from the Strait of Taiwan.[8] Given the diversity of sources and structures, it is reasonable to expect that more members will be added to the chlorosulfolipid family in the years to come.[9]

Over the past four years, several groups, including our own, have reported syntheses of members of the chlorosulfolipid family. Carreira and co-workers registered the first synthesis when they disclosed an elegant route to racemic mytilipin A.[10] Shortly thereafter, our group reported the stereochemical elucidation of danicalipin A and its synthesis in racemic form,[11] followed by the structural revision and enantioselective synthesis of malhamensilipin A.[4b,12] These three syntheses featured similar overall strategies with introduction of the polar substituents by alkene oxidation reactions.[13] The group of Yoshimitsu developed a substantially different approach, featuring their method for stereospecific deoxydichlorination of enantioenriched epoxides,[14] which culminated in clever asymmetric syntheses of both mytilipin A and danicalipin A,[15] the latter of which was contemporaneous with a third very different, creative approach from the Matsuda group.[16] Finally, the Carreira group recently reported the synthesis of the proposed structure of mytilipin B as shown in Figure 1, and came to the conclusion that this chlorosulfolipid requires stereochemical revision.[17]

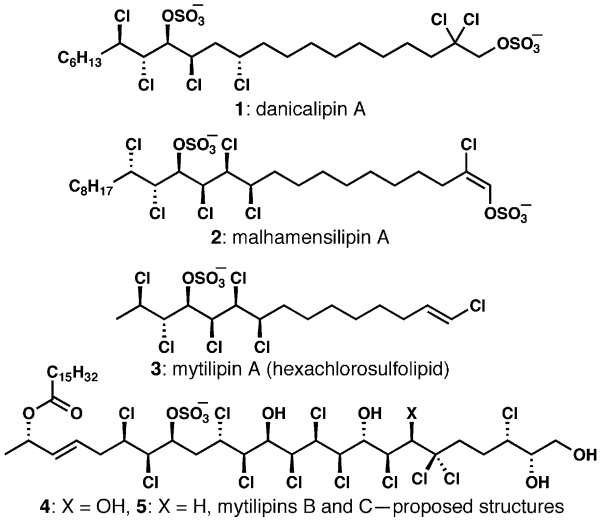

Figure 1. Representative chlorosulfolipids.

We now report a new synthesis of mytilipin A via a longest linear sequence of only seven steps for racemic material, and eight for enantioenriched chlorosulfolipid, with several key features: 1) a highly diastereoselective haloallylation of a sensitive α,β-dichloroaldehyde, 2) a kinetic resolution of a complex vinyl epoxide, 3) a convergent olefination via *Z*-selective alkene cross-metathesis, and 4) excellent levels of stereocontrol throughout.

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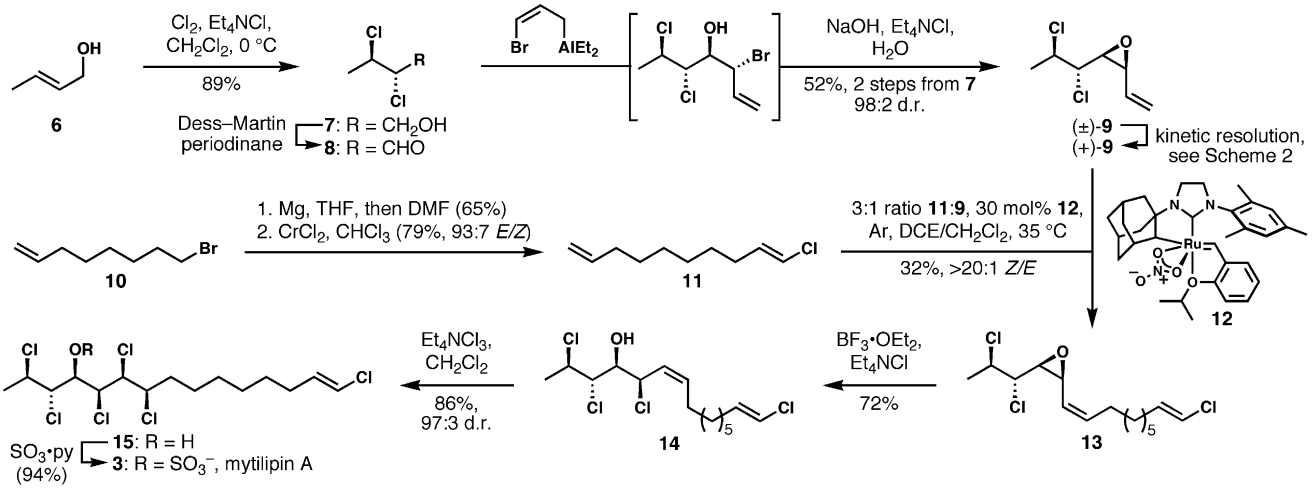


Scheme 1. Synthesis of mytilipin A via a seven-step longest linear sequence. DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

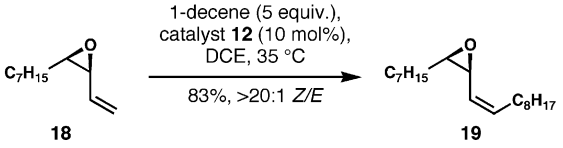
Crotyl alcohol was treated with molecular chlorine in the presence of Et_4NCl to afford *anti*-dichloride **7** (Scheme 1); presumably this procedure generates Mioskowski's reagent[18] (Et_4NCl_3) in situ. Oxidation with the Dess–Martin periodinane followed by a careful workup afforded the sensitive and volatile aldehyde **8** in crude form, which was immediately converted to vinyl epoxide **9**. The bromoallylaluminum reagent shown[19] added with high diastereocontrol, consistent with both the Felkin–Anh and Cornforth models,[20,21] and the resulting bromohydrin was converted to the epoxide upon treatment with aqueous base. The moderate yield in this case might be attributed to volatility of the intermediate aldehyde and the vinyl epoxide product; in related systems with longer alkyl chains, yields of about 75% have been obtained. Although strategically attractive in the context of the chlorosulfolipids, carbonyl addition reactions to α,β-dichloroaldehydes can be plagued by facile elimination reactions, and only Yoshimitsu et al. have previously embraced this type of C–C bond-forming reaction en route to these targets.[15] In our studies, we have found that a variety of allylation reagents that presumably react via closed transition states provide products with high levels of diastereoselectivity and without destruction of the sensitive aldehyde substrate.

The alkene partner **11** required for the convergent step was obtained in two steps from 8-bromo-1-octene. Formylation of the Grignard reagent derived from **10** followed by Takai chloroolefination[22] afforded **11** on multigram scale.

The key convergent bond formation—*Z*-selective alkene cross-metathesis[23] using the Grubbs cycloadamantyl catalyst **12**[24]—generated *Z*-vinyl epoxide **13** with complete control of alkene geometry. We attribute the relatively low yield in this particular case to catalyst deactivation by the chlorinated vinyl epoxide; however, this step compares favorably overall with previous syntheses of this type of epoxyalkene via poorly selective Wittig reactions that require several extra steps.[10–12] Unfortunately, we were unable to achieve effectively more than a single turnover with **12**;[25] however, this reaction is notable for the ability to directly introduce the vinyl chloride, which eliminates at least three post-convergence steps.[10,15a] The success of the cross-metathesis in the face of possible ring-closing metathesis (RCM) pathways can be attributed to: 1) the intrinsically slow reactivity of vinyl chlorides, 2) the slow kinetics of cyclooctene formation, and 3) the high kinetic selectivity of catalyst **12** for *Z*-alkenes, which presumably prevents reaction with the *E*-vinyl chloride in either RCM or cross-metathesis events. Vinyl epoxide chlorinolysis with inversion of configuration[11,12] proceeded smoothly under the reaction conditions shown, providing diene **14**.

Uncertain about the reactivity of the isolated vinyl chloride relative to the particularly electron-deficient allylic chloride in **14**, we were pleased to observe a completely chemoselective, highly diastereoselective (93:7 d.r. of crude reaction product, purified to 97:3), and efficient chlorination using Mioskowski's reagent. The generation of hexachloride product **15** constitutes a formal synthesis of mytilipin A, and sulfation of the secondary alcohol according to Carreira's conditions[10] completes the seven step (longest linear sequence) synthesis of racemic chlorosulfolipid. This route has enabled the preparation of over 100 mg of the target molecule to date, with a nearly 9% yield over the entire sequence. Although the final steps of the synthesis are related to those previously reported by us and the Carreira group, our rapid access to **13** takes advantage of a completely new strategy designed for general access to several of the chlorosulfolipids.

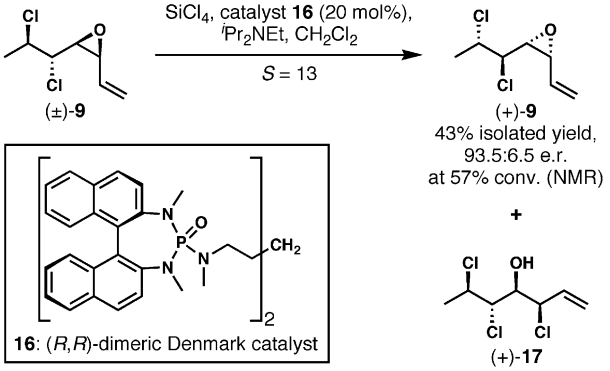
The convergent *Z*-selective alkene cross-metathesis to form **13** is noteworthy for its complete diastereoselectivity if not for its efficiency. To see if the extremely high selectivity we observed was general for vinyl epoxides, as well as to investigate the low catalytic activity of **12** with respect to the specific case in Scheme 1, we tested the reactivity of *cis*-3,4-epoxy-1-undecene (**18**) with 1-decene [Eq. (1)]. With



(1)

10 mol% of catalyst **12**, complete conversion to *Z*-vinyl epoxide **19** was observed (83% yield, >20:1 *Z*/*E*). With 1 mol% catalyst, the product was isolated in 43% yield (incomplete conversion), with equal selectivity. Therefore, it appears that vinyl epoxides are subject to highly *Z*-selective cross-metathesis with catalyst **12**, and that the poor efficiency observed in the convergent step to form **13** is likely specific to chlorinated substrates of type **9**.

In principle, adaptation of our route to the enantioselective preparation of mytilipin A simply requires access to enantioenriched dichloroalcohol **7**. However, methods for the asymmetric dichlorination of alkenes, including the allylic alcohol substrates pertinent to our synthesis, are not yet at a level of sophistication appropriate for the first step in complex molecule synthesis.[26] We contemplated accessing enantioenriched dichloroalcohols using either the stereospecific deoxydichlorination of an optically active epoxyalcohol derivative according to the method of Yoshimitsu,[14] or by resolution. Because it would add only one step to the sequence, we opted to investigate resolution strategies. Unfortunately, attempts at kinetic resolution of dichloroalcohol **7** (and dichloroaldehyde **8**) using a variety of approaches were unsuccessful; however, racemic vinyl epoxide **9** could be resolved by adapting the *meso*-epoxide desymmetrizing chlorinolysis of Denmark and co-workers (Scheme 2).[27]



Scheme 2. Kinetic resolution affords enantioenriched vinyl epoxide (+)-**9**.

The strong preference for ring opening of the vinyl epoxide at the allylic position (as opposed to the position proximal to the electron-withdrawing chloride residues) is presumably key to success. A selectivity factor of 13 was realized, allowing for material of 93.5:6.5 e.r. to be obtained at 57% conversion (by NMR analysis) and in 43% isolated yield.[28] On the basis of this result, we have defined an eight-step enantioselective synthesis of mytilipin A.[29,30] More details about this interesting resolution will be forthcoming in a full account.

A few short years ago, the highly chlorinated lipids shown in Figure 1 might have appeared to be intractable problems for chemical synthesis, because of the dearth of previous work on stereochemically complex polychlorinated compounds. Now, with the recent advances made by several groups,[10–16] and with the design and execution of our new direct synthesis described here, it has become clear that the chlorosulfolipids can be assembled in a relatively straightforward fashion. The synthesis of racemic mytilipin A that we report requires only seven linear steps from commercially available starting materials and features only productive chemical transformations. Using kinetic resolution of a vinyl epoxide, enantioenriched chlorosulfolipid can be obtained with only one additional operation. Furthermore, our synthesis demonstrates that α,β-dichloroaldehydes can participate in efficient and highly stereoselective carbonyl addition reactions, and that *Z*-selective alkene cross-metathesis is a powerful method for convergent olefination en route to the chlorosulfolipids. The successful application of these catalysts in this context further documents the ever-expanding reach of metathesis processes for stereocontrolled natural product synthesis.

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