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Authors

Chung, Won-jin

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Vanderwal, Christopher

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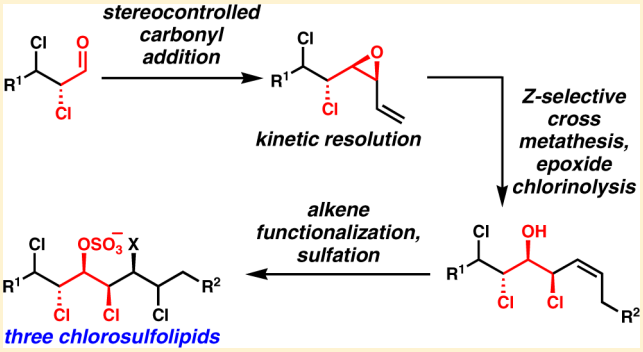
General Approach to the Synthesis of the Chlorosulfolipids Danicalipin A, Mytilipin A, and Malhamensilipin A in Enantioenriched Form

Won-jin Chung, Joseph S. Carlson, and Christopher D. Vanderwal*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025, United States

Supporting Information

ABSTRACT: A second-generation synthesis of three structurally related chlorosulfolipids has been developed. Key advances include highly stereocontrolled additions to α,β-dichloroaldehydes, kinetic resolutions of complex chlorinated vinyl epoxide intermediates, and *Z*-selective alkene cross metatheses of *cis*-vinyl epoxides. This strategy facilitated the synthesis of enantioenriched danicalipin A, mytilipin A, and malhamensilipin A in nine, eight, and 11 steps, respectively.



INTRODUCTION AND BACKGROUND

Almost 40 years after the first report of their existence,[1,2] intense activity aimed at the chemical synthesis of the chlorosulfolipids (**1**−**5**, Figure 1) began independently and essentially simultaneously in at least four research groups around the world. Apparently purely coincidental, this confluence of research might well have stemmed from the fact that truly novel and unstudied classes of natural product targets are extremely rare in current times and make very attractive research problems. Since 2009, the groups of Carreira,[3] Yoshimitsu,[4] Matsuda,[5] and our own[6] have contributed syntheses of chlorosulfolipids and, in so doing, have taken what once looked like intractable problems for synthesis and found multiple creative ways for their construction. With the exception of Carreira's tour de force synthesis of the proposed structure[2i] of mytilipin C (**5**) that determined the incorrectness of that structure,[3c] all of the published work to date has been focused on the three structurally similar chlorosulfolipids mytilipin A (**3**),[3a,4b,6e] danicalipin A (**1**),[4c,5,6b] and malhamensilipin A (**2**).[6d] At the outset of our work, we sought a general strategy toward these three targets; however, the unknown relative configuration of danicalipin A and malhamensilipin A prevented the development of such an approach at the time. Our productive collaboration with the Gerwick group unveiled the relative and absolute configuration of these two lipids[6b,c] and revealed that a "central" stereotriad was conserved among the three lipids (**1**−**3**), but that there were important differences at other centers. Indeed, the difference at C16 between danicalipin A and malhamensilipin A precluded the direct translation of our successful synthesis of the former to the latter.

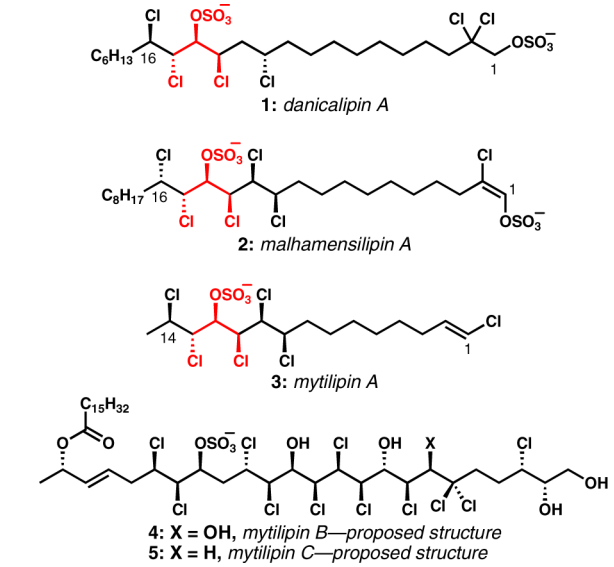


Figure 1. Representative chlorosulfolipids.

The approaches adopted for mytilipin A by Carreira[3a] and for danicalipin A and malhamensilipin A by our group[6b,d] took advantage of alkene oxidation reactions for the introduction of all of the polar atoms in the stereochemically rich regions of these targets. However, since shortly after our interest in the chlorosulfolipids began, we have been keenly interested in an approach involving diastereoselective carbonyl additions to α,β-

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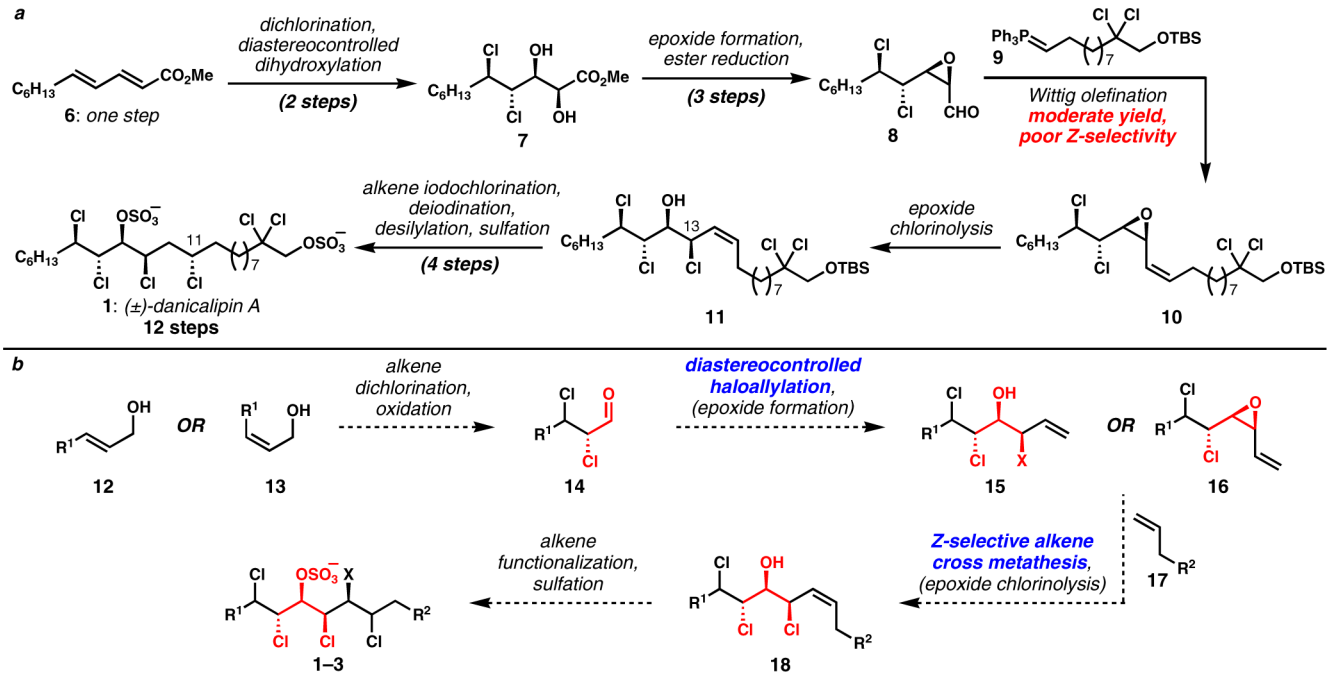
Scheme 1. *a*. Previous Synthesis of Racemic Danicalipin A. *b*. General Approach to Danicalipin A, Malhamensilipin A, and Mytilipin A Featuring Carbonyl Additions to α,β-Dichloroaldehydes and Convergent *Z*-selective Alkene Cross Metathesis



dichloroaldehydes. Conceptually, this approach was attractive because these starting materials are easy to access—at least in racemic form—and additions to the aldehyde should be highly stereocontrolled.[7] However, the poor stability of the these aldehydes, which eliminate HCl easily, prevented our early attempts to use this tactic. To our knowledge, only Yoshimitsu and co-workers had successfully added nucleophiles to α,β-dichloroaldehydes[4b,c] prior to the work that we describe here. It was that significant challenge in implementation that led us instead to the alkene oxidation approach that permitted the first syntheses of danicalipin A and malhamensilipin A.[6b,d]

Although effective, our first-generation syntheses of **1** and **2** were fraught with the several problems: (1) the critical convergent Wittig reaction was both poorly stereocontrolled and somewhat erratic in terms of reproducibility; (2) the enantioselective route to malhamensilipin A could not be applied to danicalipin A because of a stereochemical difference in the targets; and (3) the routes were longer than we had hoped. In this article, we describe the evolution of our second-generation strategy that is applicable to chlorosulfolipids **1**–**3** in enantioenriched forms by virtue of an interesting kinetic resolution of chlorinated *cis*-vinyl epoxides. This approach also obviates the troublesome Wittig reaction, which is replaced by a convergent *Z*-selective alkene cross metathesis reaction. The results are (1) for danicalipin A, eight steps racemic, nine steps enantioselective (previous best 12 steps racemic[6b] or 13 steps enantioselective[4c]); (2) for mytilipin A, seven steps racemic, eight steps enantioselective (previous best 10 steps racemic[3a,d] or 19 steps enantioselective[4b]); and (3) for malhamensilipin A, 11 steps formal enantioselective (previous best was our previous 12-step route, which was the only prior synthesis[6d]).

SYNTHESIS PLAN

To put the second-generation approach into perspective, our first synthesis of racemic danicalipin A is shown in Scheme 1a. As alluded to above, we were aiming for a shorter synthesis that could be generalized to targets **1**–**3** that obviates the troublesome Wittig olefination and that takes advantage of the common stereotriad highlighted in Figure 1. The synthesis plan that was most attractive is shown in Scheme 1b. Stereospecific *anti*-dichlorination of either an (*E*)- or a (*Z*)-allylic alcohol will lead to *anti*- or *syn*-dichloroalcohol products, respectively. Assuming high levels of 1,2-stereoinduction,[7,8] a haloallylation reaction would afford either *syn*-halohydrin **15** or *cis*-vinyl epoxide **16**, depending upon workup conditions. Either of these intermediates could be productive substrates for *Z*-selective alkene cross metathesis as a replacement for the Wittig olefination; the products that result would intersect with the late stages of our previous syntheses. The major impediments to the implementation of this plan were: (1) it was not certain that an efficient *and* stereoselective carbonyl addition to dichloroaldehydes would be possible; (2) there was no obvious way to render the synthesis enantioselective; and (3) *Z*-selective alkene cross metathesis was, at the time we began this work, very much in its infancy and was not certain to work on such unusual and potentially reactive substrates.

RESULTS AND DISCUSSION

Because of our familiarity with its late-stage chemistry, we aimed to first apply our new strategy to an enantioselective synthesis of danicalipin A. As a result, in the following sections, we will first discuss the solutions to the three key unknowns described above in the context of this target. We will then demonstrate the generality of the approach with the syntheses of all three targets in subsequent sections.

Additions to α,β-Dichloroaldehydes. For our new synthetic route, it was necessary to develop conditions for mild and highly diastereoselective haloallylation of α,β-dichloroaldehydes to establish an efficient route toward the requisite *cis*-vinyl epoxide of type **16**. In our earliest studies, attempted Grignard, organolithium, or alkali metal enolate additions to these aldehydes were met with failure, as were

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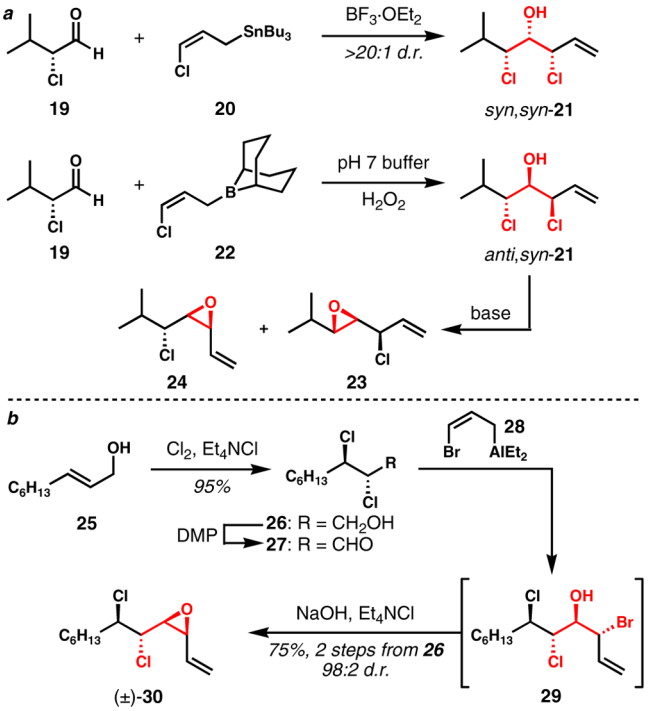
Lewis acid-catalyzed addition of π-nucleophiles. While the Yoshimitsu group had some success in this area,[4b,c] Carreira alludes to similar problems in their disclosure of the mytilipin A synthesis.[3a] On the other hand, additions to α-chloroaldehydes were generally quite efficient and often stereoselective; these outcomes were not surprising given the lack of elimination pathways and the rather well-known stereocontrol imparted by α-acceptor groups on carbonyl additions.[8] For example, the chloroallylation of α-chloroisovaleraldehyde (**19**) with (*Z*)-γ-chloroallylstannane **20**[9] in the presence of $BF_3{\cdot}OEt_2$ provided undesired *syn,syn*-**21** with high diastereoselectivity (Scheme 2a).

Scheme 2. *a*. Chloroallylation of α-Chloroaldehyde. *b*. Synthesis of Racemic *cis*-Vinyl Epoxide (±)-30



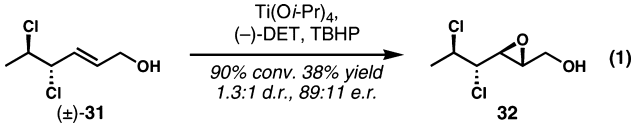
Not surprisingly, this reaction type was not successfully extended to electrophiles with β-chlorides. In contrast, **19** could be converted to desired *anti,syn*-**21** by chloroallylation with (*Z*)-γ-chloroallylborane **22**.[10] However, the base-promoted epoxide formation surprisingly proceeded with poor site selectivity to give a mixture of constitutional isomers **23** and **24**. Nonetheless, this haloallylborane reactivity could be extended to α,β-dichloroaldehydes (see below), and this outcome was the first hint that this type of electrophile tends to survive the milder conditions associated with closed transition structure allylations and related reactions. These observations were important in the eventual discovery that bromoallylaluminum reagents of type **28**[9] were optimal from the perspectives of efficiency, stereoselectivity, and ease of preparation. An attractive sequence resulted: after dichlorination of (*E*)-2-nonen-1-ol (**25**) and careful oxidation with the Dess–Martin periodinane, bromoallylation followed by basic workup afforded vinyl epoxide **30** as a single regioisomer in high yield and with essentially perfect diastereoselectivity consistent with both the Felkin–Anh and Cornforth models (Scheme 2b). This sequence could produce racemic **30** in multigram scale in about 70% yield from the commercially available allylic alcohol precursor.

Preparation of Enantioenriched Intermediates via Kinetic Resolution. Because we were clearly beholden to starting our synthesis from α,β-dichloroaldehydes, we required either enantioselective access to these key intermediates, or a means to resolve them, if we were to render our synthesis enantioselective. Although technology for asymmetric alkene chlorination is improving, with Nicolaou's recent enantioselective dichlorination of allylic alcohols[11] being particularly noteworthy, there is not currently a method that would prove economical enough in the preparation of highly enantioenriched dichloroalcohols to service a natural product synthesis endeavor of this type.

Certainly, we spent some time trying to develop just such a reaction, but with no success. Attempts to obtain enantioenriched material via enantioselective dichlorination with *Cinchona* alkaloid-derived chiral variants[12] of Mioskowski's reagent (Et_4NCl_3)[13] or resolution of dichlorinated primary alcohols by peptide-catalyzed[14] or enzymatic means were unsuccessful. Of course, highly effective examples of enzymatic resolution of chiral *primary* alcohols are few.[15]

Clearly, either resolution methods of later stage intermediates or Yoshimitsu's elegant stereospecific dichlorodeoxygenation reactions of epoxides[4a] were the most promising ways to access enantioenriched intermediates. Owing to the single additional step involved in resolutions compared with the multiple steps involved in the epoxide-based strategy, we took the former approach to solve our problem.

The Carreira group developed an asymmetric variant of their synthesis of mytilipin A (**3**) via (parallel) resolution of racemic dichloride **31** (eq 1).[3d] Sharpless asymmetric epoxidation of the



allylic alcohol functional group afforded epoxide **32** in 1.3:1 dr; the enantiopurity of the desired diastereomer was moderate at 89:11 er.

We undertook an extensive investigation into asymmetric carbonyl additions to α,β-dichloroaldehydes using chiral reagents or catalysts. The kinetic resolutions of racemic α,β-dichloroaldehyde (±)-**27** via enantioselective haloallylation with chiral Oehlschlager/Brown haloallylborane reagents (**33**/**34**)[10] proceeded with poor enantioselectivity (Scheme 3a). According to the enantioselective chloroallylation procedure of Kobayashi,[16] the chiral zinc catalyst derived from the bipyridine ligand **38** afforded the product (−)-**35** in moderate enantiopurity, and useful selectivity factors were achieved (Scheme 3b). However, the resolved starting material, which is always easier to obtain in higher enantiopurity via kinetic resolution,[17] was unstable to the reaction conditions and could not be isolated, leaving only partially resolved product **35**. Furthermore, as we showed in Scheme 2a, epoxide formation from α,α'-dichloroalcohols of type **35** was not selective, and the bromoallylation corresponding to that shown in Scheme 3b was never successfully implemented.

We next considered resolving racemic vinyl epoxide **30** derived from diastereoselective haloallylation/epoxide formation of the α,β-dichloroaldehyde (Scheme 2b). This type of vinyl epoxide was readily prepared on multigram scale and should be easily recovered after kinetic resolution. Furthermore, it has a strong bias for regiocontrol of ring opening; clearly the

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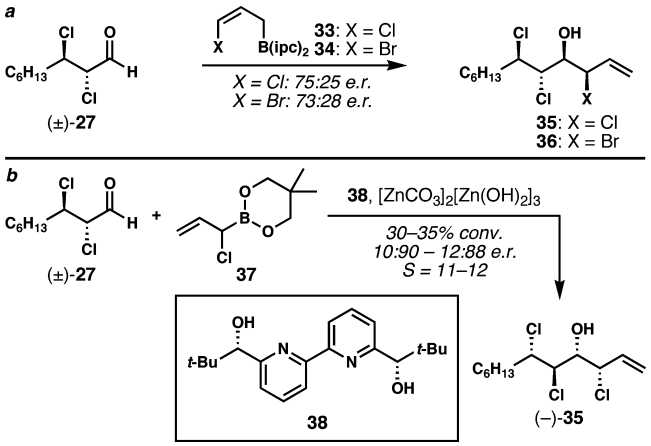
Scheme 3. *a*. Haloallylation of Dichloroaldehyde with a Chiral Boron Reagent. *b*. Chloroallylation of Dichloroaldehyde with Chiral Zinc Lewis Acid



allylic terminus is activated while the other epoxide carbon is deactivated by the proximal chlorides. Therefore, we postulated that some of the many available enantioselective *meso*-epoxide desymmetrization protocols should be plausibly extended to kinetic resolution of substrates of type **30**.

We began with Jacobsen's epoxide opening chemistry, using highly reactive (*R*,*R*)-(oligosalen)Co catalysts.[18] To the best of our knowledge, *resolutions* of internal epoxides with the Jacobsen system have not been reported; however, we felt that the *cis*-vinyl epoxide might be a close structural mimic of competent cyclic *meso*-epoxides that are frequently *desymmetrized* using Jacobsen chemistry. Surprisingly, substrate **30** proved unreactive toward nucleophiles such as water, phenol, or benzyl alcohol under published conditions for desymmetrization of *meso*-epoxides. For reasons that we do not understand, Denmark's catalytic system for desymmetrization of *meso*-epoxides via ring-opening chlorinolysis,[19a,b] using the "Lewis base activation of Lewis acids" concept,[19c] proved much more successful. In the original Denmark group study, *meso*-stilbene oxide (**39**) was effectively desymmetrized in the presence of a chiral phosphoramide Lewis base catalyst (*R*)-**40** and $SiCl_4$, a weak Lewis acid, to afford the *syn*-1,2-chlorohydrin (1*S*,2*S*)-**42** in high enantiopurity (Scheme 4a).[19a] Later, it was found that the dimeric phosphoramide Lewis base (*R*,*R*)-**41**, which is typically more selective for other $SiCl_4$-mediated enantioselective transformations, provided (1*S*,2*S*)-**42** with notably diminished enantiopurity.[19b] The stereochemical outcome of desymmetrization of *meso*-epoxide suggested that the (*R*)-BINAM-derived phosphoramde Lewis base catalysts would enrich our *cis*-vinyl epoxide reactants in the desired enantiomer by selectively catalyzing ring-opening chlorinolysis of the undesired enantiomer.

Under Denmark's conditions, the *cis*-vinyl epoxide (±)-**30** was found to be less reactive than *meso*-epoxides, probably because of the more sterically congested environment presented by the proximal chlorine bearing carbons. Consequently, the kinetic resolution with (*R*)-**40** was carried out at slightly elevated temperature (−50 °C) with higher catalyst loading (20 mol%) (Scheme 4b). Unfortunately, the resolution with (*R*)-**40** proceeded with poor selectivity (selectivity factor, S = 4). Surprisingly, in contrast to Denmark's result, the dimeric chiral Lewis base (*R*,*R*)-**41** was more selective (S = 14) for our kinetic resolution than the monomeric chiral Lewis base (*R*)-**40**. Interestingly and unexpectedly, the resolved vinyl epoxide from the kinetic resolutions with (*R*)-**40** and (*R*,*R*)-**41** were enriched in the opposite enantiomers. Other chiral Lewis bases such as *trans*-cyclohexanediamine-derived phosphoramide (*R*,*R*)-**43** and (*R*)-BINAPO ((*R*)-**44**) were also tested. These Lewis bases were more reactive than (*R*)-**40** or (*R*,*R*)-**41** but virtually unselective (S < 3). Clearly, we had a good lead with catalyst (*R*,*R*)-**41** at this point.

During the optimization of the kinetic resolution, it was found that the selectivity is highly dependent on the reaction temperature. When (±)-**30** was resolved with 10 mol% of (*R*,*R*)-**41** at −78 °C, a substantially improved selectivity factor of 33 was obtained (Table 1, entry 1). However, the reaction was even more sluggish and proceeded to only 24% conversion after 24 h. Even with higher catalyst loading (20 mol%) and extended reaction time (48 h), the conversion was improved to only 42% and the reaction became increasingly slower as the reaction progressed (entry 2). The amounts of $SiCl_4$ and *i*-Pr_2NEt seem to have little effect on the conversion and selectivity. Because it is reasonable to postulate that the rate of chlorinolysis would be increased at higher concentration of

Scheme 4. *a*. Denmark's Desymmetrization of *meso*-Epoxides. *b*. Preliminary Study of Chiral Lewis Base-Catalyzed Kinetic Resolution of *cis*-Vinyl Epoxide (±)-30. Selectivity Factor, $S = k_{fast}/k_{slow} = \ln[(1 - \text{conversion})(1 - \text{ee})]/\ln[(1 - \text{conversion})(1 + \text{ee})]$. *c*. Chiral Lewis Bases Studied for Kinetic Resolution

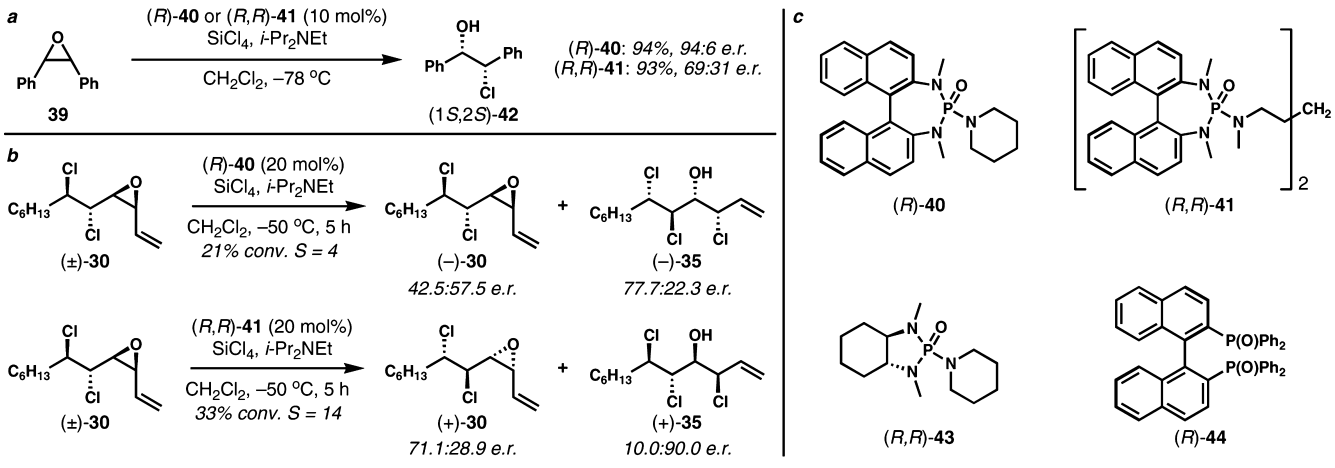


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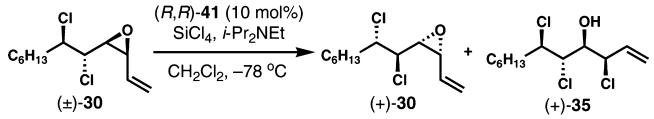
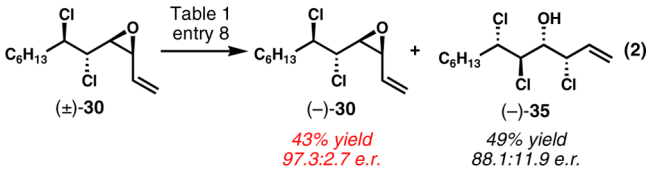
Table 1. Optimization of Kinetic Resolution of (±)-30[a]



entry	concentration (M)	time (h)	conversion[b] (%)	er (reactant)[c]	er (product)[d]	S
1	0.1	24	24	66.0:34.0	3.9:96.1	33
2[e]	0.1	48	42	84.5:15.5	5.3:94.7	37
3[f]	0.1	48	61	93.1:6.9	22.2:77.8	9
4	0.2	48	41	83.9:16.1	5.8:94.2	33
5	0.4	24	44	83.7:16.3	10.0:90.0	18
6	1.0	24	66	88.7:11.3	31.9:68.1	5
7	0.05	72	32	72.4:27.6	2.5:97.5	61
8[e,g]	0.2	24	53	2.7:97.3	88.1:11.9	27

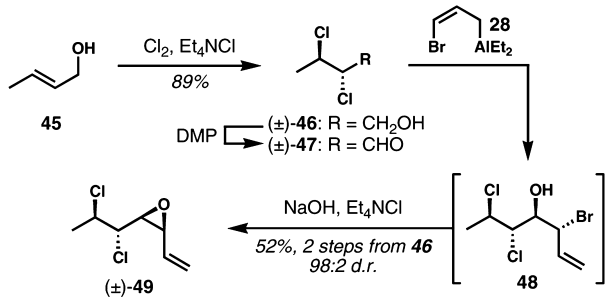
[a]All reactions employed 1.0 equiv of $SiCl_4$ and 0.1 equiv of *i*-Pr_2NEt on 0.1–2.0 mmol scale. [b]Determined by ^1H NMR analysis. [c]Determined by CSP-GC. [d]Determined by CSP-SFC after 2,4-dinitrobenzoylation. [e]20 mol% of catalyst. [f]1.0 equiv of Et_4NCl. [g]Preparative scale, using (*S*,*S*)-**41**, to preferentially recover (−)-**30**.

chloride nucleophile, the kinetic resolution was conducted in the presence of exogenous soluble chloride (entry 3). Although the conversion was improved to 61% in the presence of 1 equiv of Et_4NCl, the selectivity factor diminished significantly. It was also possible to improve the conversion by adopting higher concentrations. The kinetic resolution could be efficiently carried out at 0.2 M with little attenuation of selectivity (entry 4). The reaction could be further accelerated by further increasing the concentration; however, the selectivity factor decreased substantially (entries 5 and 6). On the other hand, the selectivity factor could be improved by performing the reaction in more diluted condition. A selectivity factor of 61 was obtained at 0.05 M even though the reaction was too slow to be practical (entry 7). Unfortunately, the mechanistic origin for the drastic effects of the exogenous chloride and the reaction concentration on the selectivity was unclear. Eventually, an ideal 53% conversion was achieved with 20 mol% of (*S*,*S*)-**41** after 24 h at 0.2 M, and the desired enantiomer of unreacted vinyl epoxide (−)-**30** was isolated in 43% yield with 97.3:2.7 er on a preparative scale (entry 8 and eq 2). The catalyst could be fully recovered after reaction.



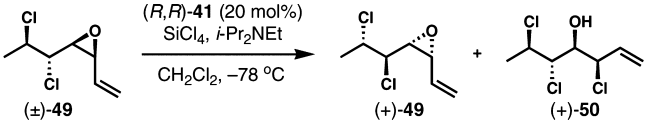
The optimized kinetic resolution conditions were next applied to a substrate that was destined for the enantioselective synthesis of mytilipin A. The *cis*-vinyl epoxide (±)-**49** was prepared in a similar manner to that used to make (±)-**30** (Scheme 5). (*E*)-Crotyl alcohol (**45**) was treated with molecular chlorine in the presence of Et_4NCl to give the *anti*-1,2-dichloride (±)-**46**. Oxidation with the Dess–Martin periodinane followed by a careful workup afforded the sensitive and volatile *α*,*β*-dichloroaldehyde (±)-**47** in crude form, which was immediately converted to volatile *cis*-vinyl epoxide (±)-**49** via bromoallylalumination and epoxide formation, again with near perfect diastereocontrol. The moderate yield in this case can be attributed to volatility of the intermediate aldehyde and the vinyl epoxide product.

Scheme 5. Synthesis of Racemic *cis*-Vinyl Epoxide (±)-49



Surprisingly, the kinetic resolution of (±)-**49**, which differs only by alkyl chain length compared to (±)-**30**, was only moderately efficient with catalyst (*R*,*R*)-**41**. Under the optimized conditions developed for (±)-**30**, a selectivity factor of only 6 was obtained (Table 2, entry 1). Although it was

Table 2. Optimization of Kinetic Resolution of (±)-49[a]



entry	concentration (M)	time (h)	conversion[b] (%)	er (reactant)[c]	S
1	0.2	24	56	84.6:16.4	6
2	0.2	36	66	92.4:7.6[d]	6
3	0.15	72	65	94.8:5.2	8
4	0.1	72	57	93.4:6.6	13

[a]All reactions employed 1.0 equiv of $SiCl_4$ and 0.1 equiv of *i*-Pr_2NEt and were conducted on 0.25–0.54 mmol scale. [b]Determined by ^1H NMR analysis. [c]Determined by CSP-GC. [d]Determined by CSP-SFC after benzoylation.

possible to recover (+)-**49** with an improved enantiopurity at higher conversion (entry 2), a more practical level of selectivity was desired. Similarly to the case of (±)-**30**, higher selectivity could be achieved at lower concentration. Consequently, the selectivity factor was improved to 8 at 0.15 M concentration (entry 3). Furthermore, a selectivity factor of 13 at 57% conversion was realized at 0.1 M concentration, and enantioenriched (+)-**49** was isolated in 93.4:6.6 er and 43%

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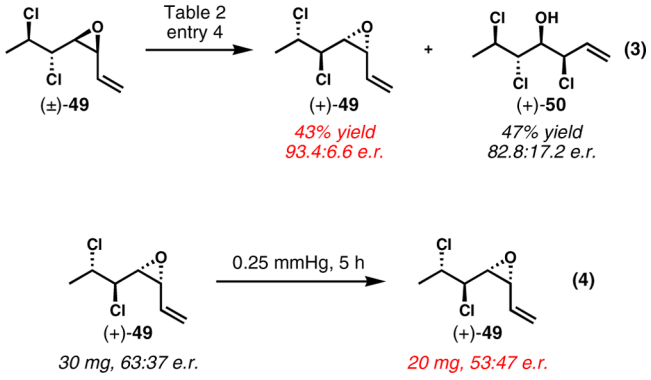
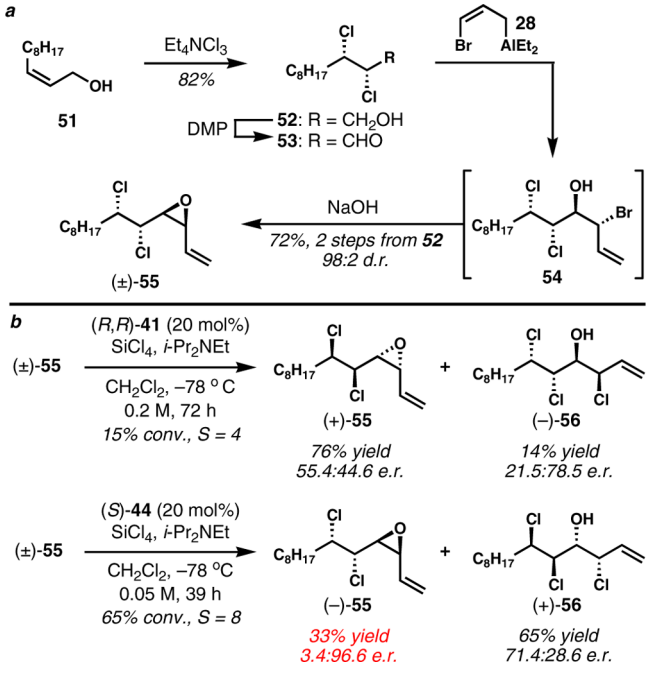
yield (entry 4 and eq 3). The monomeric phosphoramide (*R*)-**40** and (*R*)-BINAPO ((*R*)-**44**) were even less selective (*S* = ~4, not shown), although (*R*)-BINAPO was more reactive than dimeric phosphoramide catalyst (*R*,*R*)-**41**. Curiously, it was difficult to reliably analyze the enantiopurity of the chlorohydrin product (+)-**50** because of apparently facile selective sublimation of the major enantiomer under vacuum, which resulted in enantiodepletion of the sample (eq 4).[20]



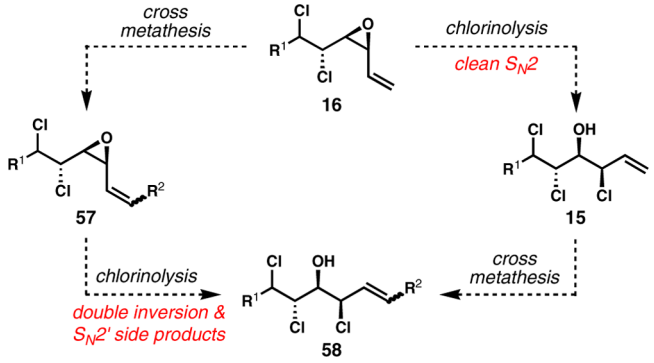
The same kinetic resolution strategy was also examined for the enantioselective synthesis of (+)-malhamensilipin A. The corresponding *cis*-vinyl epoxide (±)-**55**, which differs from substrates **30** and **49** by virtue of its *syn*-1,2-dichloride moiety, was prepared from (*Z*)-2-undecen-1-ol (**51**) via the same sequence used for previous substrates (Scheme 6a). Unfortunately, (±)-**55** was considerably less reactive toward chlorinolysis than the other vinyl epoxide substrates, and the enantioselectivity was very poor (Scheme 6b). Under the general conditions with 20 mol% of (*R*,*R*)-**41**, the resolution proceeded to only 15% conversion even after 72 h and afforded a selectivity factor of only 4. Modified reaction conditions with higher concentrations, higher temperatures, or addition of exogenous chloride, while likely to accelerate the reaction, would equally likely attenuate the already very low enantioselectivity, as we had previously observed in the study of (±)-**30**. When (±)-**55** was resolved with the typically more reactive (*S*)-BINAPO ((*S*)-**44**), a much higher reaction rate was indeed observed. Contrary to previous cases, the selectivity factor was also improved, although it was still moderate (*S* = 8–9). From a preparative scale reaction, the resolved vinyl epoxide (−)-**55** was obtained in 3.4:96.6 er and 34% yield. Several related chiral bis(phosphine oxide)s such as (*S*)-Tol-BINAPO, (*S*)-H_8-BINAPO, and (*R*)-SEGPHOS dioxide were also tested, but the selectivity was not improved.

Scheme 6. *a*. Synthesis of Racemic *cis*-Vinyl Epoxide (±)-55. *b*. Kinetic Resolution of (±)-55



Two different orders of operations were considered for alkene cross metathesis and ring-opening chlorinolysis (Scheme 7). The left-hand sequence involves the alkene cross metathesis of a vinyl epoxide (**16**) followed by chlorinolysis of the resulting internal alkenyl epoxide, which might be plagued by double inversion at the allylic center and S_N2' side reactions, as seen in previous studies. On the other hand, the right-hand sequence is initiated with chlorinolysis of the terminal vinyl epoxide, which might proceed as a clean S_N2 reaction under certain conditions, for example, the "racemic version" of the vinyl epoxide chlorinolysis resolution using $SiCl_4$ and an achiral Lewis base catalyst such as HMPA. The resulting allylic chlorohydrin **15** would then be a potential substrate for subsequent alkene cross metathesis to deliver **58**. With the latter sequence, the enantioenriched 1,2-chlorohydrin product from the kinetic resolution could also be conveniently utilized for the synthesis of enantiomeric chlorosulfolipids.

Scheme 7. Possible Orders of Operations for Alkene Cross Metathesis and Ring-Opening Chlorinolysis



Electron-poor allylic chloride (±)-**35** underwent alkene cross metathesis with 1-decene in the presence of 10 mol% of the

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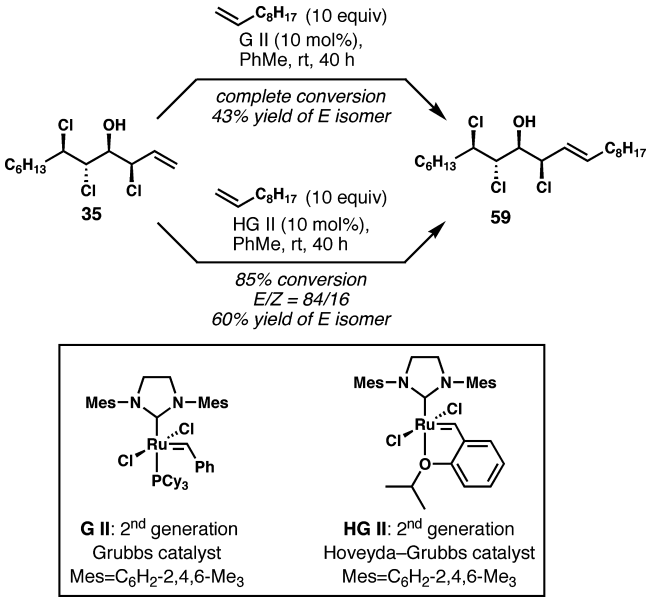
Grubbs second-generation catalyst (**G II**) at room temperature to afford the (*E*)-alkene product **59** in 43% yield along with dimeric side products (Scheme 8); because of the relatively

Scheme 8. Alkene Cross Metathesis of (±)-35

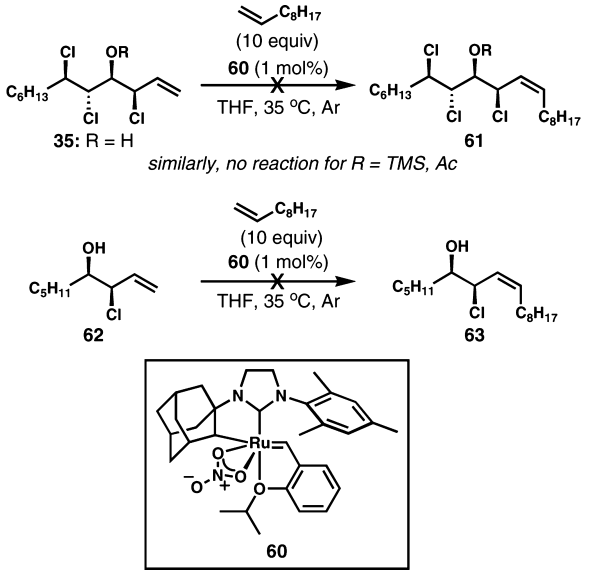


complex crude reaction mixture, it was difficult to determine the inherent *E*/*Z* selectivity of this reaction. The Hoveyda–Grubbs second-generation catalyst (**HG II**) promoted slower but cleaner alkene cross metathesis to give an 84:16 *E*:*Z* mixture of alkene isomers in 85% conversion and 60% yield of isomerically pure **59**. Unfortunately, iodochlorination of **59** with ICl provided a complex crude mixture (not shown), in contrast to the case of the corresponding *Z*-isomer that had been iodochlorinated with high efficiency in our first-generation approach, although with low diastereoselectivity. Attempts to directly hydrochlorinate the unactivated alkene under iron-mediated radical hydrofunctionalization conditions recently reported by Boger[22] was also unsuccessful, probably because of the low reactivity of the electron-deficient alkene.

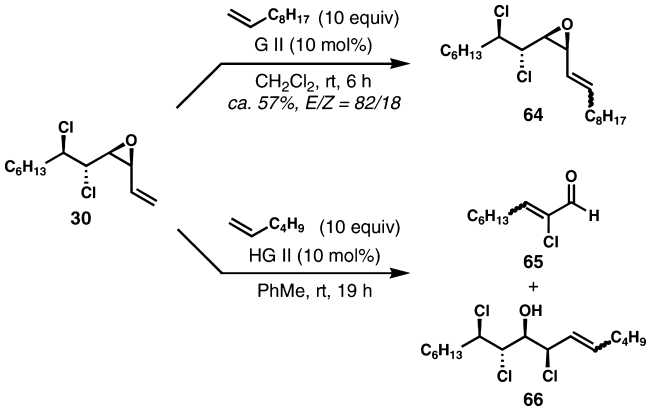
To generate the more desirable (*Z*)-alkene isomer, *Z*-selective alkene cross metathesis of allylic chloride **35** with various terminal alkene partners in the presence of recently developed Grubbs cycloadamantyl catalyst **60**,[23] which was generously provided first by the Grubbs group and later by Materia, was investigated. However, not only **35** but also hydroxy-protected substrates and the less chlorinated substrate **62** exhibited no reactivity (Scheme 9). Ruthenium metathesis catalysts are clearly able to execute cross metatheses of allylic chlorides; at this stage, we have no reasonable understanding of the apparent limitation of the *Z*-selective catalysts toward allylic chlorides, nor do we know if it is a truly general limitation.

Alternatively, the corresponding *cis*-vinyl epoxide was examined as a substrate for alkene cross metathesis. Similarly to the corresponding allylic chloride, *cis*-vinyl epoxide (±)-**30** underwent alkene cross metathesis with 1-decene in the presence of 10 mol% of **G II** to afford **64** with moderate 82:18 *E*:*Z*-selectivity (Scheme 10). Unlike the case of chlorohydrin substrates, it was difficult to separate the internal alkenyl epoxide product from the unreacted terminal vinyl epoxide reactant. These compounds were isolated as a mixture (estimated yields of the product and the recovered reactant:

Scheme 9. Alkene Cross Metathesis of 35 with *Z*-Selective Catalyst 60



Scheme 10. Alkene Cross Metathesis between 30 and Simple Terminal Alkenes



~57 and 10%, respectively based on NMR integration). In contrast, a complex mixture was obtained from the similar reaction with **HG II**. While the desired product was not detected, one of the major components in the crude mixture was identified as the unsaturated chloroaldehyde **65**, which implies the formation of α,β-dichloroaldehyde **27** (Scheme 2b) under the reaction conditions. Additionally, the presence of chlorohydrin **66** as a minor component in the crude mixture further suggests the formation of **27** followed by elimination of HCl, which is presumably responsible for epoxide chlorinolysis of a small amount of desired alkene cross metathesis product. The formation of **65** was confirmed from the reactions between **30** and **HG II** (10 and 100 mol%) in the absence of other metathesis partners. At this stage, we cannot put forth a reasonable mechanism for this interesting three-carbon degradation of vinyl epoxides. We have not investigated the generality of this reaction type.

Gratifyingly, *cis*-vinyl epoxide **30** turned out to be a competent substrate for *Z*-selective alkene cross metathesis. In the presence of 1 mol% of catalyst **60**, **30** underwent alkene cross metathesis with an excess of 1-hexene to 12% conversion at 35 °C in 1 h (Scheme 11). The *Z*-isomer of vinyl epoxide **67**

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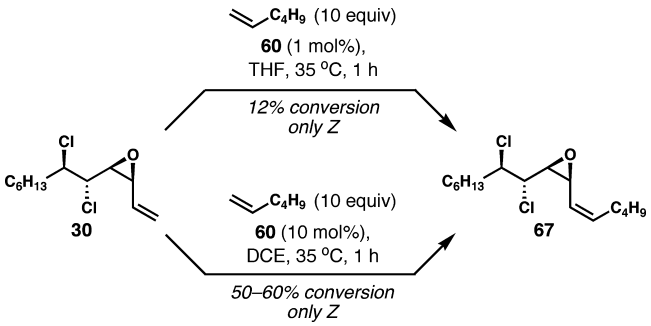
Scheme 11. *Z*-Selective Alkene Cross Metathesis of 30 with 1-Hexene



was produced with exquisite selectivity. Such exceptionally high *Z*-selectivity had only been rarely observed with this catalyst.[23] Other solvents such as toluene or dichloromethane had no significant impact on the conversion and selectivity. The catalytic activity was typically lost within a few hours, and the reactions would proceed no further. The conversion could be improved to about 50−60% (NMR estimate) with higher loading of catalyst (10 mol%), and the use of chlorinated solvents such as dichloromethane or 1,2-dichloroethane proved beneficial because of the poor solubility of **60** in other solvents. However, the decomposition of the starting vinyl epoxide was a serious side reaction, and significant amounts of an as yet unidentified decomposition product were formed.

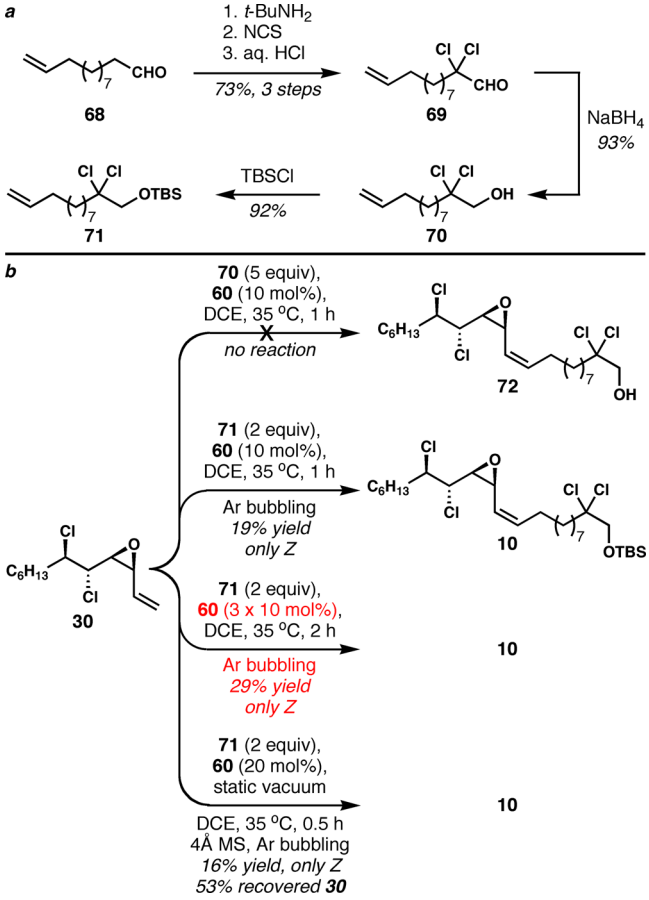
With this preliminary success in hand, we turned to the use of the relevant alkene **71** as the metathesis partner, which was made from known aldehyde **68**[24] via a slight modification of Yoshimitsu's procedure[4c] as shown in Scheme 12a. This high molecular weight compound could not be used in as large excess as the model alkenes owing to effects on reaction concentration; initial reactions suffered from very low efficiencies, and the decomposition of the starting vinyl epoxide remained problematic. The related alkene **70**, with a free hydroxyl group and attendant lower molecular weight that could potentially be used in greater excess, was unreactive (Scheme 12b).

To achieve higher conversion and suppress the decomposition, an extensive optimization of the reaction conditions was conducted. A variety of reaction solvents including tetrahydrofuran, diethyl ether, *t*-butyl methyl ether, toluene, chlorobenzene, hexafluorobenzene,[25] α,α,α-trifluorotoluene,[25] and octafluorotoluene,[25] as well as neat conditions were employed, but the reaction efficiency was not improved. The reaction was even slower at room temperature, and performing the reaction at higher temperature (60 °C) only resulted in greater decomposition.

A wide range of additives were also evaluated. Amine bases such as *i*-Pr_2NEt and di-*tert*-butylpyridine promoted decomposition. 1,4-Benzoquinone, known to scavenge ruthenium hydride species[26] that might be formed during reaction and cause decomposition, only attenuated the catalytic reactivity of **60**. The reaction became slightly cleaner in the presence of 3 or 4 Å molecular sieves, but substrate decomposition could not be completely avoided. $Ti(O\textit{i}\text{-}Pr)_4$[27] and hexachloroethane,[28] which have been used to improve the reactivity of other alkene cross metathesis reactions, had no influence on the reaction.

Portionwise addition of catalyst and 1-hexene also provided no advantage. We hoped that removal of ethylene from the reaction mixture would shift the cross metathesis equilibrium

Scheme 12. *a*. Preparation of Potential Alkene Cross Metathesis Partners 70 and 71 for the Synthesis of Danicalipin A and Malhamensilipin A. *b*. *Z*-Selective Alkene Cross Metathesis of 30 for the Synthesis of Danicalipin A (all compounds shown are racemic)



and drive these reactions to higher conversion. Therefore, the reaction was carried out under static vacuum, continuous vacuum, and in an open vessel inside a glovebox, but to no avail. More rigorous removal of ethylene was attempted by vigorously bubbling argon through the reaction mixture, and gratifyingly, the formation of the unknown was finally prevented. Under optimized conditions, with 10 mol% of **60**, (±)-**10** was obtained in 19% yield along with 74% recovered starting material (Scheme 12b). It was more challenging to suppress the decomposition with higher catalyst loadings, and the mass balance was poorer. The decomposition could be minimized by slowing down the reaction rate via a portionwise addition of catalyst, giving the product **10** in 29% yield with 40% recovered starting material using 30 mol% of **60**. Although we were unable to achieve more than the equivalent of a single turnover, this sequence still stands as a marked improvement over the previous Wittig-based route. Access to enantioenriched **10** now requires only five steps, compared with our previous eight-step approach that afforded racemic material. As a result, this moderate success completed a much shorter, enantioselective formal synthesis of danicalipin A because of the interception of intermediate **10** from our first-generation synthesis. However, more improvements in the end-game were still possible (see below).

Convergent *Z*-selective alkene cross metathesis for mytilipin A with the corresponding *cis*-vinyl epoxide **49** proceeded

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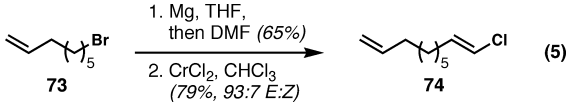
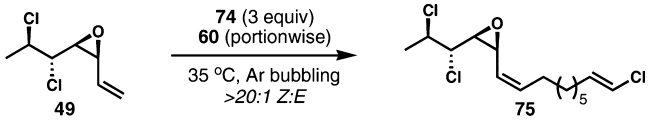
similarly to the corresponding reaction for danicalipin A. Alkene metathesis partner **74** was obtained in two steps from 8-bromo-1-octene (**73**) via formylation of Grignard reagent followed by Takai-Utimoto chloroolefination (eq 5). The



(5)

convergent metathesis reactions were carried out with vigorous bubbling of argon to prevent the decomposition of starting vinyl epoxide, and the desired alkene (±)-(*Z*)-**75** was produced as a single geometrical isomer. Again, we were unable to achieve more than a single turnover with 10−30 mol% of catalyst **60** (Table 3, entries 1 and 2). The use of fluorinated

Table 3. *Z*-Selective Alkene Cross Metathesis for the Synthesis of Mytilipin A[a]



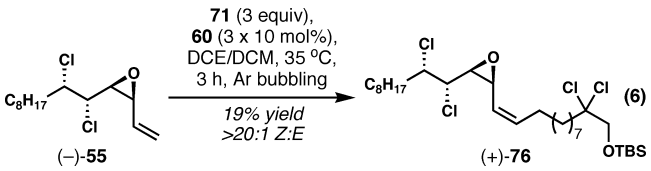
entry	**60** (mol%)	solvent	time (h)	yield (%)
1	10	DCE/CH_2Cl_2	2	10
2	30	DCE/CH_2Cl_2	3	32
3	30	$PhCF_3$/CH_2Cl_2	3	33
4	50	$PhCF_3$/CH_2Cl_2	4	34
5[b]	100	DCE	3	39

[a]All reactions were carried out on 0.15−0.25 mmol scale. [b]5 equiv of **74** was employed. Catalyst **60** was added in one portion.

solvents such as α,α,α-trifluorotoluene[25] did not result in any improvement (entry 3). Unfortunately, higher loading of catalyst only resulted in significant loss of mass balance and the yield of product was only marginally improved (entries 4 and 5). Despite the low efficiency of the *Z*-selective alkene cross metathesis, the direct incorporation of the vinyl chloride is a marked improvement over previous syntheses because it eliminates at least three postconvergence steps. Cross metathesis partner **74** might appear upon cursory analysis to be poised for side reactivity because as a 1,9-diene cyclooctene formation could occur via ring-closing metathesis. However, vinyl chlorides are relatively slow to react in metathesis processes, and cyclo-octene formation can also be a sluggish reaction. Almost certainly, however, the high kinetic selectivity of catalyst **60** for (*Z*)-alkenes is presumably the most important factor that prevents reaction with the (*E*)-vinyl chloride in either RCM or cross metathesis events.

Unfortunately, the convergent *Z*-selective alkene cross metathesis was even less efficient for malhamensilipin A. The metathesis product (+)-**76** was isolated only in 19% yield from the reaction of (−)-**55** with **71** under the analogous conditions to those used for danicalipin A (eq 6). Cursory attempts to improve the efficiency of this reaction were unsuccessful. For reasons explained below, the improvement of this convergent step was not a priority.

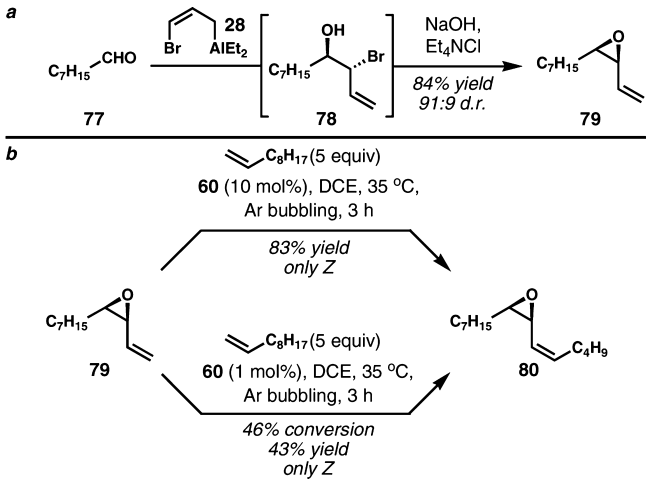
While admittedly not as efficient as desired, the convergent *Z*-selective alkene cross metathesis is noteworthy for its complete diastereoselectivity in all cases examined. To see if the extremely high selectivity we observed was general for *cis*-vinyl epoxides, as well as to investigate the low catalytic activity



(6)

of **60** with respect to the specific chlorinated cases relevant to the chlorosulfolipids, we tested the reactivity of unchlorinated *cis*-vinyl epoxide **79** with 1-decene (Scheme 13). In the

Scheme 13. *a*. Synthesis of Simple Vinyl Epoxide 79. *b*. *Z*-Selective Alkene Cross Metathesis of (±)-79



presence of 10 mol% of **60**, complete conversion to (*Z*)-vinyl epoxide **80** was observed (83% isolated yield, >20:1 *Z*:*E*). Even with only 1 mol% of catalyst, the reaction proceeded to 46% conversion and the product was isolated in 43% yield with equal selectivity. Therefore, it appears that *cis*-vinyl epoxides are subject to highly *Z*-selective alkene cross metathesis with **60**, and that the poor efficiency observed in the convergent steps for chlorosulfolipids is likely specific to chlorinated substrates. Recently, the Grubbs group also demonstrated that vinyl epoxides are excellent substrates for *Z*-selective metathesis using these catalysts.[23o]

Postconvergent Manipulations and Completion of the Syntheses. Completion of the synthesis of (+)-danicalipin A took advantage of a similar reaction sequence to that previously developed in the context of our first-generation approach (Scheme 1a). Lewis acid-mediated chlorinolysis of the internal alkenyl epoxide **10** typically afforded a diastereomeric mixture of the desired S_N2 product **11** and the double inversion[3a,6b] product **81** as well as the constitutional isomer **82** formed via S_N2' substitution (Scheme 14a). The extent of side product formation was highly dependent on the choice of Lewis acid and the concentration of chloride anion. Because exclusive S_N2 reactivity was observed from the reaction of terminal *cis*-vinyl epoxide with $SiCl_4$ in the presence of HMPA, a combination of $SiCl_4$ and a number of Lewis base activators including pyridine, DMAP, pyridine *N*-oxide, HMPA, DMPU, DMI, and TMU was evaluated with or without Et_4NCl. In all cases, a variable amount of side products were produced and a useful level of selectivity was not accomplished (90:10−31:69 dr, 2−50% S_N2'). Both undesired pathways were reasonably attenuated when the epoxide was opened using dry HCl; however, high selectivity was desired specifically for the

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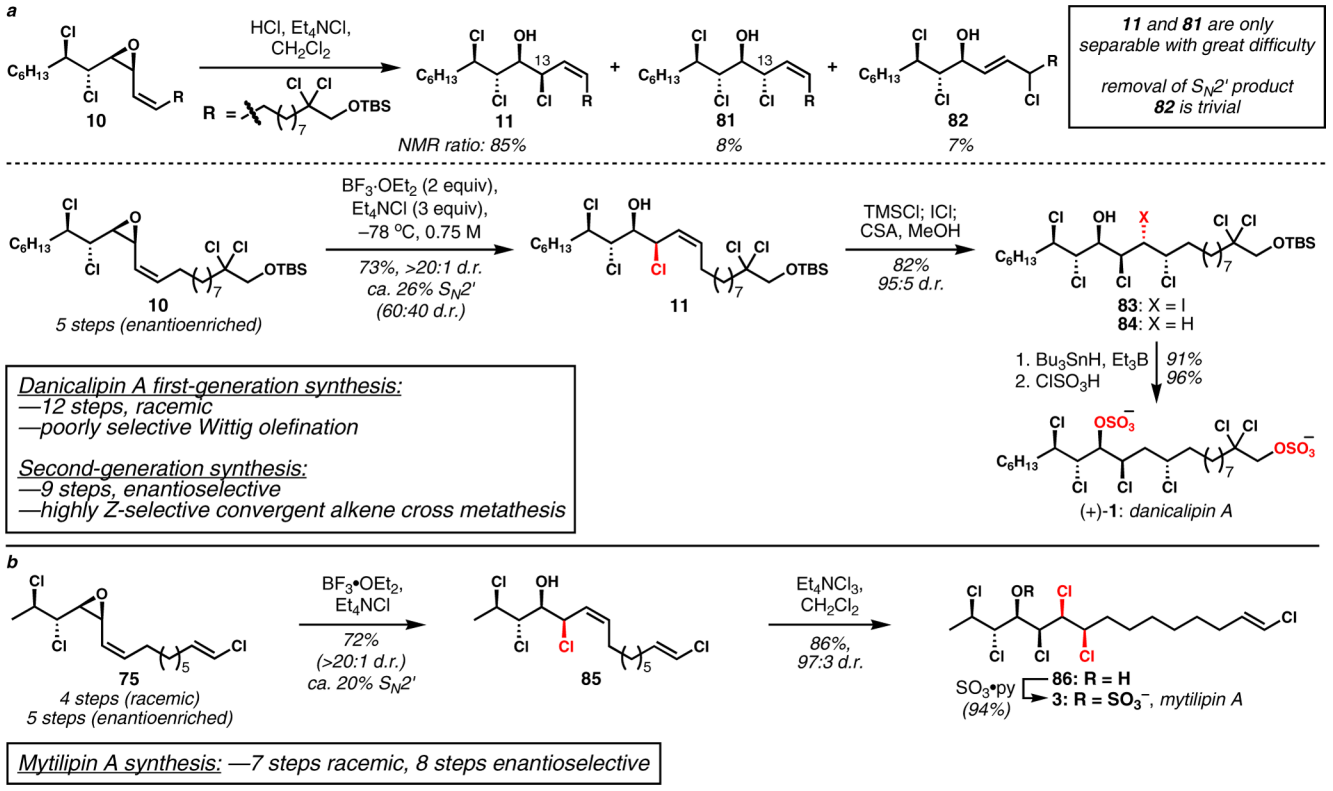
Scheme 14. *a*. Completion of the Synthesis of (+)-Danicalipin A. *b*. Completion of the Synthesis of (−)-Mytilipin A



exclusion of double inversion product **81**, which is more difficult to separate from the desired product. Double inversion could be completely overcome by employing $BF_3{\cdot}OEt_2$ at −78 °C with a high concentration of Et_4NCl. Despite the presence of a rather large amount of S_N2' product **82**, the desired isomer **11** could be isolated in 73% yield as a single diastereomer. A major problem of our first-generation synthesis was the poorly diastereoselective iodochlorination reaction of **11** (~1.8:1 dr), which was compounded further by the very painstaking separation of diastereomers at that stage or after deiodination. We found that transient introduction of a trimethylsilyl group on the C14 hydroxyl permitted high diastereocontrol (95:5 dr) in the iodochlorination, and because the silyl group could be introduced and removed in the same pot, this result had a significantly positive impact on the synthesis. Overall, the new approach facilitated a nine-step synthesis of enantioenriched (+)-danicalipin A (4.6% overall yield), which is a significant improvement over our 12-step racemic first-generation synthesis.

Completion of the synthesis of mytilipin A required only three postconvergence steps (Scheme 14b). $BF_3{\cdot}OEt_2$-mediated vinyl epoxide chlorinolysis with inversion of configuration proceeded with exclusive diastereoselectivity and delivered diene **85**. Dichlorination of the electron-deficient allylic chloride afforded hexachloride **86** in 86% yield with high diastereoselectivity (93:7 dr of crude product, purified to 97:3) and complete chemoselectivity with respect to the isolated vinyl chloride. Sulfation of the secondary alcohol according to Carreira's conditions[3a] completed the synthesis of mytilipin A. In this way, racemic chlorosulfolipid could be accessed in 8.6% yield over the seven linear steps sequence, and enantioenriched mytilipin A is available via a longest linear sequence of eight steps (3.7% overall yield). These results compare favorably to the previously reported syntheses.

It is indeed fortuitous that we chose to first pursue danicalipin A with this new approach. The choice of malhamensilipin A as a first target could easily have discouraged us from pursuing this strategy. Although, as described above, this strategy led to much improved syntheses of mytilipin A and danicalipin A, there was ultimately little improvement in the synthesis of malhamensilipin A, for which we had already established an enantioselective synthesis, via the same number of steps, and for which the Wittig reaction was not improved upon with the metathesis option. Therefore, while we are pleased to claim a formal enantioselective synthesis of malhamensilipin A as part of this second-generation, general strategy for chlorosulfolipid synthesis, we would suggest that our first enantioselective synthesis of this single target would likely be the preferred method to access samples of this natural product. However, if new catalysts become available that can better effect these challenging *Z*-selective cross metatheses, and if a truly effective method for asymmetric dichlorination of allylic alcohols is discovered, the strategy described here would be hard to beat for any of these three chlorosulfolipid targets. Indeed, this approach has the distinct advantage that it can be rendered enantioselective without recourse to resolution once asymmetric catalysis technology is developed for allylic alcohol dichlorination.

■ CONCLUSIONS

We have developed a concise and general approach for the enantioselective synthesis of three chlorosulfolipid targets that takes strategic advantage of a common stereotriad. Diastereoselective carbonyl addition to sensitive α,β-dichloroaldehydes, *Z*-selective alkene cross metatheses, and kinetic resolution of

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chlorinated vinyl epoxides are key advances that permitted success in this second-generation approach. Enantioenriched danicalipin A, mytilipin A, and malhamensilipin A are accessed in nine, eight, and 11 steps, respectively.

Given the paucity of efforts toward this class of natural products until about five years ago, it is remarkable that so many effective solutions to these targets from multiple research groups have appeared in such short order. Certainly, polychlorinated natural products are not to be feared as objectives for chemical synthesis and are rather well-behaved in the contexts of many different reaction types. We look forward to extending our efforts toward other polyhalogenated natural products.

EXPERIMENTAL SECTION

General Experimental Protocols. All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvents including dichloromethane, toluene, *N*,*N*-dimethylformamide, and tetrahydrofuran were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Dichloroethane (DCE) was heated to reflux over CaH_2 for 3 h, distilled under argon, and stored over 3 Å molecular sieves prior to use. Column chromatography was performed using 60 Å (0.040−0.063 mm) mesh silica gel (SiO_2). The following reagents were distilled from the indicated drying agents under argon prior to use: 2,2,6,6-tetramethylpiperidine (Na), allyl bromide (CaH_2), triethylamine (CaH_2), *N*,*N*-diisopropylethylamine (CaH_2), trimethylsilyl chloride (TMSCl, CaH_2), and ethylene diamine (CaH_2). Silicon tetrachloride was heated at reflux for 2 h under a flow of argon and then distilled prior to use. *Z*-Selective Grubbs cycloadamantyl catalyst (**60**, Materia) was stored in the glovebox and used as received. Dimeric Denmark catalysts ((*R*,*R*)-**41** and (*S*,*S*)-**41**, Obiter) were used as received and recovered by recrystallization from boiling benzene. (*E*)-2-Nonen-1-ol (**25**), boron trifluoride diethyl etherate, and tri-*n*-butyltin hydride were distilled prior to use. Tetraethylammonium chloride was heated to reflux in benzene with a Dean−Stark trap for 3 h and dried at 0.25 mmHg before use. Chlorine gas, Dess−Martin periodinane, diethylaluminum chloride, *n*-butyllithium, imidazole, iodine monochloride (1.0 M in CH_2Cl_2), camphorsulfonic acid (CSA), triethylborane (1.0 M in THF), chlorosulfonic acid, nickel(II) acetate tetrahydrate, sodium borohydride, magnesium (20−100 mesh), 1,2-dibromoethane, 1-bromo-10-undecene, *N*-chlorosuccinimide, *t*-butyldimethylsilyl chloride, and paraformaldehyde were used without further purification. Tetraethylammonium trichloride[13] and (*S*)-BINAPO[29] were prepared according to literature procedures.

^1H and ^{13}C spectra were referenced to residual solvent ($CDCl_3$: 7.26 ppm, ^1H, 77.00 ppm, ^{13}C; CD_3OD: 3.31 ppm, ^1H, 49.00 ppm, ^{13}C). Chemical shifts are reported in parts per million, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), and app (apparent). Coupling constants, *J*, are reported in Hertz. Infrared (IR) spectra were recorded on an FT-IR instrument on NaCl plates, and peaks are reported in cm^{-1}. High-resolution mass spectra (HRMS) data are reported in the form of (*m*/*z*). Kugelrohr distillation temperatures reported are air bath temperatures (ABT). Visualization of analytical thin-layer chromatography was accomplished with UV(254) and potassium permanganate ($KMnO_4$) or *p*-anisaldehyde staining solutions. Optical rotation data were obtained on a digital polarimeter and are reported as follows: concentration (*c* = g/100 mL) and solvent. Analytical gas chromatography (CSP-GC) was performed on a gas chromatograph equipped with a flame ionization detector and a dimethylated *β*-cyclodextrin (B-DM, 30 m) capillary column. The injector temperature and the detector temperature were 200 °C with a split ratio of approximately 100:1.

Synthesis of Danicalipin A. ***(±)-(2S,3R)-2,3-Dichloro-1-nonanol (26):***[4c] To a stirred solution of Et_4NCl (6.63 g, 40.0 mmol)[30] and (*E*)-2-nonen-1-ol (2.84 g, 20.0 mmol) in CH_2Cl_2 (60 mL) was bubbled Cl_2 at 0 °C until the reaction mixture turned yellow (∼2 min). Ethylene was bubbled until the yellow color disappeared (∼2 min). The resulting colorless solution was diluted with CH_2Cl_2 (50 mL) and shaken with a mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were shaken with saturated aqueous NaCl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 123−126 °C) to afford (±)-**26** (4.04 g, 95%, contained ∼1.5% of 1,3-dichloro-2-nonanol) as a colorless oil. Data for (±)-**26**: ^1H NMR (600 MHz, $CDCl_3$) *δ* 4.12 (app td, *J* = 8.7, 8.7, 2.7 Hz, 1H), 4.09−4.06 (m, 1H), 4.024 (d, *J* = 6.6 Hz, 1H), 4.017 (d, *J* = 6.6 Hz, 1H), 2.11−2.02 (m, 1H), 1.97 (app t, *J* = 6.9, 6.9 Hz, 1H), 1.82−1.75 (m, 1H), 1.64−1.54 (m, 1H), 1.48−1.39 (m, 1H), 1.39−1.23 (m, 6H), 0.89 (dd, *J* = 6.8, 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 66.4, 64.5, 61.8, 34.9, 31.6, 28.6, 25.5, 22.5, 14.0; IR (thin film) 3390, 2924, 2858, 1463, 1455, 1434, 1379, 1066, 725, 655 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_9H_{18}{}^{35}Cl_2ONH_4$ $[M + NH_4]^+$ 230.1078, found 230.1071.

(±)-(2S,3R)-2,3-Dichlorononanal (27): To a stirred suspension of (±)-**26** (2.13 g, 10.0 mmol) and $NaHCO_3$ (2.52 g, 30.0 mmol) in CH_2Cl_2 (10 mL, saturated with H_2O) was added Dess−Martin periodinane (6.36 g, 15.0 mmol) slowly over 1 min at 0 °C under air. After stirring for 10 min, the ice bath was removed and the reaction mixture was stirred at rt for 30 min prior to the addition of *n*-pentane (100 mL). The resulting mixture was filtered, washed with saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg) to give **27** (1.99 g) as a pale yellow oil. The crude material was used directly for the next reaction without further purification (∼3% 2-chloro-2-nonenal).[31] Data for (±)-**27**: ^1H NMR (600 MHz, $CDCl_3$) *δ* 9.43 (d, *J* = 3.1 Hz, 1H), 4.25 (dd, *J* = 7.4, 3.1 Hz, 1H), 4.24−4.21 (m, 1H), 2.02−1.97 (m, 1H), 1.84−1.77 (m, 1H), 1.63−1.54 (m, 1H), 1.48−1.39 (m, 1H), 1.39−1.27 (m, 6H), 0.90 (dd, *J* = 6.9, 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 191.4, 64.9, 59.8, 34.0, 31.5, 28.5, 25.5, 22.5, 14.0; IR (thin film) 2926, 2858, 1734, 1458 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_9H_{15}{}^{35}ClONH_4$ $[M - HCl + NH_4]^+$ 192.1155, found 192.1158.

(±)-(3S,4S,5S,6R)-5,6-Dichloro-3,4-epoxy-1-dodecene (30): To a stirred solution of TMP (3.71 mL, 22.0 mmol) in THF (50 mL) was added *n*-BuLi (2.50 M in hexanes, 8.40 mL, 21.0 mmol) at −78 °C. After being stirred for 30 min, the LiTMP solution was cannulated into a solution of allyl bromide (1.82 mL, 21.0 mmol) and Et_2AlCl (1.0 M in hexanes, 40.0 mL, 40.0 mmol) in THF (100 mL) at −78 °C over 5 min. The resulting solution was stored at −78 °C, while (±)-**27** was prepared (see above). A solution of (±)-**27** in THF (10 mL + rinsed with 5 mL × 2) was added dropwise over 15 min. After being stirred at −78 °C for 4 h, the reaction mixture was poured into an ice-cold 5 M aq NaOH solution (200 mL). Et_4NCl (17 mg, 0.10 mmol) was added.[32] The biphasic mixture was vigorously stirred at rt for 1 h prior to the dilution with *n*-pentane (100 mL) and filtration. The organic layer was separated, and the aqueous layer was extracted with *n*-pentane (100 mL × 2). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (200 mL × 2), dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 5.0 cm, *l* = 13.5 cm, *n*-pentane/CH_2Cl_2, 9/1, R_f = 0.29, *p*-anisaldehyde) and bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 123−127 °C) to give (±)-**30** (1.89 g, 75% from (±)-**26**, 98:2 dr) as a colorless oil. Data for (±)-**30**: ^1H NMR (600 MHz, $CDCl_3$) *δ* 5.82 (ddd, *J* = 17.1, 10.6, 5.6 Hz, 1H), 5.52 (d, *J* = 17.1 Hz, 1H), 5.45 (d, *J* = 10.7 Hz, 1H), 4.21 (ddd, *J* = 9.4, 4.6, 4.1 Hz, 1H), 3.76 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.57 (app t, *J* = 4.9, 4.9 Hz, 1H), 3.46 (dd, *J* = 9.0, 4.3 Hz, 1H), 1.98−1.87 (m, 2H), 1.65−1.59 (m, 1H), 1.47−1.39 (m, 1H), 1.36−1.26 (m, 6H), 0.89 (dd, *J* = 6.9, 6.9 Hz, 3H); ^{13}C NMR (126 MHz,

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$CDCl_3$) δ 130.4, 121.2, 65.2, 60.6, 57.7, 56.0, 34.5, 31.6, 28.6, 26.5, 22.5, 14.0; IR (thin film) 2956, 2928, 2858, 1463, 1455, 1250, 981, 934, 783, 668, 597 cm^{-1}; HRMS (CI-TOF) m/z calcd for $C_{12}H_{20}{}^{35}Cl_2ONH_4$ $[M + NH_4]^+$ 268.1235, found 268.1236.

(−)-(3S,4S,5S,6R)-5,6-Dichloro-3,4-epoxy-1-dodecene (30), (−)-(3S,4R,5R,6S)-3,5,6-trichloro-1-dodecen-4-ol (35): To a stirred solution of (±)-**30** (126 mg, 0.502 mmol) and (*S*,*S*)-**41** (84 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) were added *i*-Pr_2NEt (9 μL, 0.05 mmol) and $SiCl_4$ (57 μL, 0.50 mmol) at −78 °C. After 24 h, a solution of $CH_3OH/Et_3N/CH_2Cl_2$ (1/1/5, 4 mL) was added quickly at −78 °C. The resulting solution was vigorously stirred with a saturated aqueous $NaHCO_3$ solution (20 mL) at rt for 2 h prior to filtration. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). (*S*,*S*)-**41** was recovered from the residue by column chromatography (SiO_2, ϕ = 2.2 cm, l = 7 cm, CH_2Cl_2/*i*-PrOH, 10/1, R_f = 0.37, UV). The fractions that contained **30** and **35** were combined and purified by column chromatography (SiO_2, ϕ = 2.2 cm, l = 11 cm, *n*-pentane/CH_2Cl_2, 8/1 to 4/1, *p*-anisaldehyde) to give (−)-**35** (70 mg, 49%, R_f = 0.12 in 8/1, 88.1:11.9 er) as a colorless oil and (−)-**30** as a colorless oil, which was purified again by column chromatography (54 mg, 43%, R_f = 0.30 in 8/1, 2.7:97.3 er). Data for (−)-**30**: $[\alpha]_D{}^{26}$ = −29.9 (*c* 1.00, $CHCl_3$); GC (B-DM, 30 psi, 145 °C) t_R 15.5 min (2.7%), 16.5 min (97.3%). Data for (−)-**35**: $[\alpha]_D{}^{25}$ = −60.6 (*c* 1.00, $CHCl_3$); GC (B-DM, 30 psi, 165 °C) t_R 18.5 min (88.1%), 19.1 min (11.9%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (ddd, J = 16.9, 10.2, 7.7 Hz, 1H), 5.49 (d, J = 16.9 Hz, 1H), 5.35 (d, J = 10.2 Hz, 1H), 5.07 (d, J = 7.6 Hz, 1H), 4.51 (app dt, J = 10.5, 2.7, 2.7 Hz, 1H), 4.31 (dd, J = 9.4, 2.7 Hz, 1H), 3.89 (app td, J = 9.8, 9.8, 1.3 Hz, 1H), 2.23 (d, J = 9.9 Hz, 1H), 1.92−1.83 (m, 1H), 1.83−1.74 (m, 1H), 1.68−1.58 (m, 1H), 1.46−1.23 (m, 7H), 0.89 (app t, J = 6.6, 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4, 119.6, 74.5, 66.5, 65.0, 62.5, 32.4, 31.6, 28.6, 26.5, 22.6, 14.0; IR (thin film) 3540, 2956, 2927, 2857, 1465, 1379, 1265, 1096, 1069, 987, 935 cm^{-1}; HRMS (CI-TOF) m/z calcd for $C_{12}H_{21}{}^{35}Cl_3ONH_4$ $[M + NH_4]^+$ 304.1002, found 304.1000.

(+)-(11Z,13S,14S,15S,16R)-1-tert-Butyldimethylsiloxy-2,2,-15,16-tetrachloro-13,14-epoxy-11-docosene (10):[6b] The solvents were bubbled with argon for 15 min before use. To a stirred solution of (−)-**30** (52 mg, 0.21 mmol) and **71** (152 mg, 0.414 mmol) in DCE (210 μL) in a test tube (12 mm × 75 mm) was added a solution of **60** (39 mg, 0.062 mmol) in CH_2Cl_2 (210 μL) in three portions (0, 0.5, 1.0 h) at 35 °C while the reaction mixture was vigorously bubbled with argon (saturated with DCE).[33] After being stirred at 35 °C with argon bubbling for an additional 2 h, the reaction mixture was cooled to rt, filtered through silica gel (ϕ = 2.2 cm, l = 9 cm, CH_2Cl_2, 40 mL), and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 3.8 cm, l = 15 cm, *n*-pentane/CH_2Cl_2, 8/1, R_f = 0.24, *p*-anisaldehyde) to give (+)-**10** (35 mg, 29%, >20:1 = *Z*:*E*) as a colorless oil. Data for (+)-**10**: $[\alpha]_D{}^{26}$ = +14.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (app dt, J = 10.9, 7.6 Hz, 7.6, 1H), 5.26−5.20 (m, 1H), 4.21 (ddd, J = 9.6, 4.4, 4.0 Hz, 1H), 3.92 (s, 2H), 3.76 (dd, J = 9.1, 4.0 Hz, 1H), 3.74 (dd, J = 7.9, 4.3 Hz, 1H), 3.44 (dd, J = 9.1, 4.2 Hz, 1H), 2.27−2.19 (m, 2H), 2.19−2.14 (m, 2H), 1.99−1.86 (m, 2H), 1.66−1.55 (m, 3H), 1.46−1.39 (m, 3H), 1.39−1.26 (m, 14H), 0.91 (s, 9H), 0.89 (app t, J = 6.9, 6.9 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 121.5, 93.5, 72.1, 65.2, 61.5, 57.4, 52.5, 43.5, 34.3, 31.6, 29.29, 29.27, 29.26, 29.1, 29.0, 28.6, 28.1, 26.5, 25.7, 24.7, 22.5, 18.3, 14.0, −5.4.

(+)-(7R,8S,9S,10R,11Z)-22-tert-Butyldimethylsiloxy-7,8,10,21,-21-pentachloro-11-docosen-9-ol (11):[6b] To a stirred solution of (+)-**10** (35 mg, 0.059 mmol) and Et_4NCl (30 mg, 0.18 mmol) in CH_2Cl_2 (240 μL) was added $BF_3{\cdot}OEt_2$ (15 μL, 0.12 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was poured into an ice-cold saturated aqueous $NaHCO_3$ solution (10 mL). To the biphasic mixture were added CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 1.5 cm, l = 9 cm, *n*-pentane/CH_2Cl_2, 5/1 to 3/1 to 1/1, *p*-anisaldehyde) to give (+)-**11** (27 mg, 73%, R_f = 0.25 in 3/1, >20:1 dr) as a colorless oil and S_N2' product **82** (9.6 mg, 26%, R_f = 0.33 and 0.24 in 1/1, 6:4 dr) as a colorless oil. Data for (+)-**11**: $[\alpha]_D{}^{25}$ = +62.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (app t, J = 10.3, 10.3 Hz, 1H), 5.66 (app dt, J = 10.7, 7.4, 7.4 Hz, 1H), 5.38 (dd, J = 9.9, 1.7 Hz, 1H), 4.49 (app dt, J = 10.3, 2.9, 2.9 Hz, 1H), 4.29 (dd, J = 9.0, 3.1 Hz, 1H), 3.92 (s, 2H), 3.83−3.78 (m, 1H), 2.34 (d, J = 10.5 Hz, 1H), 2.21−2.09 (m, 4H), 1.91−1.83 (m, 1H), 1.83−1.76 (m, 1H), 1.67−1.62 (m, 1H), 1.61−1.56 (m, 2H), 1.46−1.36 (m, 3H), 1.36−1.25 (m, 14H), 0.91 (s, 9H), 0.89 (app t, J = 6.8, 6.8 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.7, 125.8, 93.5, 75.1, 66.8, 62.4, 60.1, 43.5, 32.5, 31.6, 29.3, 29.2, 29.1, 29.0 (2C), 28.6, 27.6, 26.5, 25.7, 24.7, 22.6, 18.3, 14.0, −5.4. Data for **82** (a 6:4 mixture of diastereomers): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97−5.90 (m, 1H), 5.79 (ddd, J = 15.2, 13.9, 6.8, 1H), 4.77 (app td, J = 7.3, 7.3, 3.9 Hz, 0.4H), 4.72 (app td, J = 7.2, 7.2, 4.3 Hz, 0.6H), 4.39 (app quintet, J = 7.4, 7.4, 7.4, 7.4 Hz, 1H), 4.18 (ddd, J = 8.8, 6.7, 4.1 Hz, 1H), 3.92 (s, 2H), 3.91−3.88 (m, 1H), 2.20−2.14 (m, 2H), 2.13−2.04 (m, 2H), 1.89−1.73 (m, 3H), 1.65−1.51 (m, 3H), 1.50−1.37 (m, 3H), 1.37−1.23 (m, 14H), 0.91 (s, 9H), 0.89 (app t, J = 6.8, 6.8 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.0, 135.7, 128.22, 128.17, 93.5, 72.1, 72.0, 71.7, 69.4, 69.1, 61.9, 61.7, 61.6, 43.5, 38.4, 38.3, 34.7, 34.5, 31.6, 29.30, 29.26, 29.0, 28.9, 28.61, 28.60, 26.43, 26.35, 25.7, 25.3, 25.2, 24.7, 22.5, 18.3, 14.1, −5.4; IR (thin film) 3403, 2929, 2857, 1463, 1256, 1153, 1120, 970, 840, 780 cm^{-1}.; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{53}{}^{35}Cl_5O_2SiNa$ $[M + Na]^+$ 647.2155, found 647.2143.

(−)-(11S,12R,13S,14R,15S,16R)-1-tert-Butyldimethylsiloxy-2,2,-11,13,15,16-hexachloro-14-hydroxy-12-iododocosane (83):[6b] To a stirred solution of (+)-**11** (27 mg, 0.043 mmol) and imidazole (8.8 mg, 0.13 mmol) in CH_2Cl_2 (430 μL) was added TMSCl (11 μL, 0.086 mmol) at rt. After being stirred for 10 min, the reaction mixture was cooled to −78 °C and ICl (1.0 M in CH_2Cl_2, 215 μL, 0.215 mmol) was added. After being stirred for 20 min at −78 °C, a solution of CSA (100 mg, 0.43 mmol) in CH_3OH (645 μL) was added and the cold bath was removed. After being stirred for 30 min, the brown solution was poured into a stirred mixture of saturated aqueous $NaHCO_3$ solution (5 mL) and saturated aqueous $Na_2S_2O_3$ solution (5 mL). The resulting colorless biphasic mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 1.1 cm, l = 5.5 cm, *n*-pentane/CH_2Cl_2, 5/1 to 3/1, R_f = 0.29 in 3/1, *p*-anisaldehyde) to give (−)-**83** (28 mg, 82%, 95:5 dr) as a colorless oil. Data for (−)-**83**: $[\alpha]_D{}^{26}$ = −7.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.98 (d, J = 10.9 Hz, 1H), 4.72 (app t, J = 10.6, 10.6 Hz, 1H), 4.56 (dd, J = 10.9, 1.8 Hz, 1H), 4.48 (app dt, J = 10.5, 2.6, 2.6 Hz, 1H), 4.38 (dd, J = 9.8, 2.4 Hz, 1H), 3.92 (s, 2H), 3.75−3.71 (m, 1H), 2.19−2.16 (m, 2H), 2.14 (d, J = 11.3 Hz, 1H), 2.04−1.97 (m, 1H), 1.97−1.88 (m, 1H), 1.83−1.78 (m, 1H), 1.77−1.71 (m, 1H), 1.69−1.62 (m, 1H), 1.62−1.56 (m, 2H), 1.53−1.46 (m, 1H), 1.46−1.38 (m, 3H), 1.38−1.27 (m, 13H), 0.92 (s, 9H), 0.90 (app t, J = 6.8, 6.8 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 93.5, 74.6, 72.1, 66.3, 66.0, 62.9, 62.8, 43.5, 42.6, 40.6, 32.8, 31.6, 29.2 (2C), 29.0, 28.9, 28.6, 26.6, 26.2, 25.7, 24.7, 22.6, 18.3, 14.1, −5.3.

(+)-(11S,13S,14R,15S,16R)-1-tert-Butyldimethylsiloxy-2,2,-11,13,15,16-hexachloro-14-hydroxydocosane (84):[6b] Toluene was bubbled with argon for 20 min before use. To a stirred solution of (−)-**83** (28 mg, 0.035 mmol) in toluene (355 μL) were added *n*-Bu_3SnH (11 μL, 0.041 mmol, 99% pure by ^{1}H NMR in C_6D_6)[34] and Et_3B (1.0 M in THF, 7 μL, 0.007 mmol) at −78 °C. After being stirred for 2 h at −78 °C, *n*-pentane (3.55 mL) was added and the resulting solution was concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 1.1 cm, l = 5.5 cm, *n*-pentane/CH_2Cl_2, 1/0 to 4/1, R_f = 0.25 in 4/1, *p*-anisaldehyde) to give (+)-**84** (21.5 mg, 91%) as a colorless oil. Data for (+)-**84**: $[\alpha]_D{}^{25}$ =

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+34.3 (*c* 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 4.96 (d, *J* = 10.3 Hz, 1H), 4.51 (app dt, *J* = 10.6, 2.4, 2.4 Hz, 1H), 4.30 (dd, *J* = 9.7, 2.4 Hz, 1H), 4.17−4.13 (m, 1H), 3.92 (s, 2H), 3.77 (app t, *J* = 10.7, 10.7 Hz, 1H), 2.35−2.28 (m, 1H), 2.20−2.16 (m, 2H), 2.16 (d, *J* = 11.6 Hz, 1H), 2.02−1.95 (m, 1H), 1.94−1.85 (m, 1H), 1.83−1.73 (m, 3H), 1.68−1.62 (m, 1H), 1.62−1.57 (m, 2H), 1.57−1.49 (m, 1H), 1.49−1.39 (m, 2H), 1.39−1.26 (m, 14H), 0.91 (s, 9H), 0.89 (app t, *J* = 6.8, 6.8 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 93.5, 75.1, 72.1, 66.5, 63.0, 62.7, 60.4, 44.3, 43.5, 38.7, 32.4, 31.6, 29.3, 29.2, 29.0 (2C), 28.6, 26.6, 26.2, 25.7, 24.7, 22.6, 18.3, 14.0, −5.3.

(+)-Danicalipin A Disodium Salt (1):.[2k,5,4c,6b] To a stirred solution of (+)-**84** (21.5 mg, 0.0324 mmol) in CH_2Cl_2 (650 μL) was added $ClSO_3H$ (5 drops) via a Pasteur pipet at rt under air. After being stirred for 10 min, the reaction mixture was slowly poured into a vigorously stirred mixture of a saturated aqueous $NaHCO_3$ solution (6.5 mL) and solid $NaHCO_3$ (650 mg). The resulting heterogeneous mixture was diluted with EtOH (26 mL), filtered, and concentrated in vacuo (30 mmHg). The residue was suspended in THF (20 mL), filtered, and concentrated in vacuo (25 mmHg). The residue purified by column chromatography (SiO_2, ϕ = 2.2 cm, *l* = 14.5 cm, CH_2Cl_2/CH_3OH, 3/1, R_f = 0.38, *p*-anisaldehyde) to give (+)-**1** (23.4 mg, 96%) as a colorless amorphous solid. Data for (+)-**1**: $[\alpha]_D^{25}$ = +34.2 (*c* 2.34, CH_3OH) (lit. $[\alpha]_D^{26}$ +33.0 (*c* 0.40, CH_3OH),[4c] $[\alpha]_D^{28}$ +31.5 (*c* 0.25, CH_3OH),[5] $[\alpha]_D^{25}$ +12.8 (*c* 0.2, CH_3OH)[2k]); ^1H NMR (600 MHz, CD_3OD) δ 4.89 (d, *J* = 11.2 Hz, 1H), 4.75 (d, *J* = 10.7 Hz, 1H), 4.55 (d, *J* = 10.2 Hz, 1H), 4.45 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.31 (s, 2H), 4.23−4.19 (m, 1H), 2.56−2.49 (m, 1H), 2.27−2.24 (m, 2H), 2.15−2.06 (m, 1H), 1.99−1.92 (m, 1H), 1.85−1.76 (m, 2H), 1.76−1.69 (m, 1H), 1.69−1.62 (m, 2H), 1.61−1.52 (m, 2H), 1.51−1.42 (m, 2H), 1.42−1.27 (m, 14H), 0.90 (app t, *J* = 6.9, 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD, 313 K) δ 91.3, 80.9, 75.6, 68.4, 63.3, 62.4, 62.2, 45.5, 45.1, 39.9, 33.5, 32.9, 30.4, 30.3, 30.07, 30.05, 30.0, 27.6, 27.4, 25.8, 23.6, 14.4. The analytical data for (+)-**1** were in agreement with the data given in refs 2k, 4c, 5, and 6b.

Synthesis of Malhamensilipin A. ***(Z)-2-Undecen-1-ol (51):*** To a stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (9.12 g, 36.7 mmol) in CH_3OH (500 mL) was added $NaBH_4$ (1.38 g, 36.7 mmol) portionwise over 5 min at 0 °C. The blue solution immediately turned black upon addition of $NaBH_4$. After being stirred for an additional 5 min, the ice bath was removed and ethylene diamine (4.90 mL, 36.7 mmol) was added. After being stirred for 5 min, a solution of undec-2-yn-1-ol[35] (24.7 g, 147 mmol) in CH_3OH (230 mL) was added. The reaction mixture was quickly purged with H_2 three times and stirred overnight under a balloon of H_2 prior to the dilution with H_2O (100 mL) and *n*-pentane (100 mL). After filtration through Celite, the organic layer was separated and the aqueous layer was extracted with *n*-pentane (100 mL × 3). The combined organic extracts were washed with H_2O (50 mL) and saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (5 mmHg) to afford **51** (25.0 g, 98%) as a colorless oil. The crude material was used for the next reaction without any further purification. Data for **51**: ^1H NMR (600 MHz, $CDCl_3$) δ 5.62−5.52 (m, 2H), 4.19 (d, *J* = 6.4 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.38−1.32 (m, 2H), 1.32−1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5, 128.4, 58.8, 32.0, 29.8, 29.6, 29.42, 29.38, 27.6, 22.8, 14.3; IR (thin film) 3347, 3938, 3857, 1015 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_{11}H_{22}ONH_4$ $[M + NH_4]^+$ 188.2014, found 188.2023.

(±)-(2S,3S)-2,3-Dichloro-1-undecanol (52): To a stirred solution of (4.96 g, 29.1 mmol) in CH_2Cl_2 (70 mL) was added Et_4NCl_3 (13.8 g, 58.3 mmol) portionwise over 5 min at rt. After the yellow color disappeared over the course of 10 min, another portion of Et_4NCl_3 (6.89 g, 29.1 mmol) was added portionwise over 3 min. After being stirred for 30 min, the reaction mixture was poured into a mixture of saturated aqueous $NaHCO_3$ solution (15 mL) and saturated aqueous $Na_2S_2O_3$ solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (30 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (150 mL of SiO_2, 10% EtOAc/hexanes, R_f = 0.6 in 30% EtOAc/hexanes, $KMnO_4$) to give (±)-**52** (5.79 g, 82%) as a colorless oil. Data for (±)-**52**: ^1H NMR (500 MHz, $CDCl_3$) δ 4.22 (ddd, *J* = 8.1, 5.4, 2.6 Hz, 1H), 4.18 (m, 1H), 3.95 (ddd, *J* = 11.9, 7.7, 6.0 Hz, 1H), 3.89 (ddd, *J* = 12.1, 7.5, 5.6 Hz, 1H), 1.94 (dd, *J* = 7.7, 5.4 Hz, 1H), 1.90−1.84 (m, 2H), 1.57−1.51 (m, 1H), 1.44−1.22 (m, 11H), 0.88 (app t, *J* = 6.6, 6.6 Hz, 3H); ^{13}C (126 MHz, $CDCl_3$) δ 65.6, 64.7, 62.2, 35.3, 32.0, 29.5, 29.3, 29.1, 26.7, 22.8, 14.3; IR (thin film) 3363, 3923, 2855, 1455, 1041 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_{11}H_{22}{}^{35}Cl_2ONH_4$ $[M + NH_4]^+$ 258.1392, found 258.1401.

(±)-(2S,3S)-2,3-Dichloroundecanal (53): To a stirred suspension of (±)-**52** (2.20 g, 9.12 mmol) and $NaHCO_3$ (2.30 g, 27.4 mmol) in CH_2Cl_2 (46 mL, saturated with H_2O) was added Dess−Martin periodinane (5.80 g, 13.7 mmol) portionwise over 1 min at 0 °C under air. After being stirred for 5 min, the ice bath was removed and the reaction mixture was stirred at rt for 25 min prior to the addition of hexanes (20 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (50 mL × 3). The combined organic extracts were filtered, dried over $MgSO_4$, filtered, and concentrated in vacuo (5 mmHg) to give (±)-**53** as a pale yellow oil. The crude material was generally used directly for the next reaction within 30 min and without further purification (it was often contaminated with up to 5% 2-chloro-2-undecenal). Data for (±)-**53**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 4.40 (app s, 2H), 1.92−1.86 (m, 2H), 1.55−1.48 (m, 1H), 1.40−1.22 (m, 11H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 67.0, 60.1, 35.1, 31.8, 29.3, 29.1, 28.8, 26.1, 22.6, 14.1; IR (thin film) 2927, 2856, 1736, 1465 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{11}H_{19}{}^{35}ClONa$ $[M - HCl + Na]^+$ 225.1022, found 225.1013.

(±)-(3S,4S,5S,6S)-5,6-Dichloro-3,4-epoxy-1-tetradecene (55): To a stirred solution of TMP (3.39 mL, 20.1 mmol) in THF (46 mL) was added *n*-BuLi (2.47 M in hexanes, 7.75 mL, 19.2 mmol) at −78 °C. After being stirred for 15 min, the LiTMP solution was cannulated into a solution of allyl bromide (1.66 mL, 19.2 mmol) and Et_2AlCl (1.0 M in hexanes, 36.5 mL, 36.5 mmol) in THF (46 mL) at −78 °C over 15 min. The resulting solution was stored at −78 °C, while (±)-**53** was prepared (see above). A solution of (±)-**53** in THF (10 mL + rinsed with 8 mL × 2) was added dropwise down the side of the flask. After being stirred at −78 °C for 5 h, the cooling bath was removed and a 6 M aq NaOH solution (100 mL) was added. After stirring vigorously for 1 h, the biphasic mixture was diluted with hexanes (100 mL) and shaken in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with hexanes (100 mL × 3). The combined organic extracts were washed with saturated aqueous NaCl solution (50 mL × 3), filtered through silica gel (CH_2Cl_2, 300 mL), and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (500 mL of SiO_2, 5% CH_2Cl_2/hexanes, R_f = 0.2, $KMnO_4$) and bulb-to-bulb distillation under reduced pressure (0.1 mmHg, ABT 150 °C) to give (±)-**55** as a colorless oil (1.83 g, 72% from (±)-**52**). Data for (±)-**55**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.0, 10.6, 5.3 Hz, 1H), 5.49 (d, *J* = 17.2 Hz, 1H), 5.45 (d, *J* = 10.7 Hz, 1H), 4.26 (ddd, *J* = 8.3, 4.9, 2.7 Hz, 1H), 3.67 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.64 (app t, *J* = 4.7 Hz, 1H), 3.54 (dd, *J* = 9.7, 4.7 Hz, 1H), 1.94 (app dtd, *J* = 14.2, 9.5, 4.8 Hz, 1H), 1.83, (app ddt, *J* = 14.0, 10.1, 5.4 Hz, 1H), 1.58−1.50, (m, 1H), 1.43−1.35 (m, 1H), 1.35−1.22 (m, 10H), 0.88 (app t, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 130.5, 121.3, 63.5, 60.4, 58.6, 57.4, 35.8, 32.0, 29.5, 29.3, 29.1, 26.5, 22.8, 14.3; IR (thin film) 2926, 2855, 932 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_{14}H_{24}{}^{35}Cl_2ONH_4$ $[M + NH_4]^+$ 296.1548, found 296.1560.

(−)-(3S,4S,5S,6S)-5,6-Dichloro-3,4-epoxy-1-tetradecene (55), (+)-(3S,4R,5R,6R)-3,5,6-trichloro-1-tetradecen-4-ol (56): To a stirred solution of (±)-**55** (500 mg, 1.79 mmol) and (*S*)-BINAPO (234 mg, 0.358 mmol) in CH_2Cl_2 (36 mL) were added *i*-Pr_2NEt (31.0 μL, 0.179 mmol) and $SiCl_4$ (144 μL, 1.25 mmol) slowly at −78 °C. After 39 h, a solution of $CH_3OH/Et_3N/CH_2Cl_2$ (1/1/5, 5 mL) was added quickly at −78 °C. The resulting solution was vigorously stirred with a saturated aqueous $NaHCO_3$ solution (20 mL) at rt for 2 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo (5 mmHg). The residue

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was purified by column chromatography (SiO_2, 5% EtOAc/hexanes, $KMnO_4$) to give (−)-**55** (165 mg, 33%, 3.4:96.6 er, R_f = 0.7 in 10% EtOAc/hexanes) as a colorless oil and (+)-**56** (367 mg, 65%, 71.4:28.6 er, R_f = 0.5 in 10% EtOAc/hexanes) as pale yellow crystals. The enantiopurity of the recovered reactant (−)-**55** was measured after ring-opening chlorinolysis to form (−)-**56**. Data for (−)-**55**: $[\alpha]_D^{25}$ = −23.5 (*c* 1.74, $CHCl_3$); GC (B-DM, 30 psi, 180 °C) t_R 23.9 min (2.6%), 25.1 min (97.4%). Data for (+)-**56**: mp 34.0−36.0 °C; $[\alpha]_D^{24}$ = +1.6 (*c* 2.01, $CHCl_3$); GC (B-DM, 30 psi, 180 °C) t_R 23.7 min (71.4%), 25.3 min (28.6%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.07 (ddd, *J* = 17.1, 10.3, 7.4 Hz, 1H), 5.49 (dd, *J* = 16.1, 1.0 Hz, 1H), 5.35 (dd, *J* = 10.3, 0.8 Hz, 1H), 5.10 (dd, *J* = 7.4, 1.0 Hz, 1H), 4.56 (ddd, *J* = 9.0, 5.2, 1.4 Hz, 1H), 4.10 (dd, *J* = 9.4, 1.5 Hz, 1H), 4.05 (dd, *J* = 9.1, 1.1 Hz, 1H), 2.18 (d, *J* = 8.8 Hz, 1H), 2.00 (app dtd, *J* = 14.0, 10.0, 4.7 Hz, 1H), 1.80 (app ddt, *J* = 15.5, 10.7, 5.5 Hz, 1H), 1.58−1.51 (m, 1H), 1.45−1.38 (m, 1H), 1.36−1.24 (m, 10H), 0.89 (app t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9, 119.5, 74.5, 64.7, 64.5, 61.7, 36.5, 32.0, 29.5, 29.3, 29.2, 26.7, 22.8, 14.3; IR (thin film) 3390, 2925, 2855, 933 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{14}H_{25}{}^{35}Cl_4O$ [M + Cl]$^-$ 349.0659, found 349.0665.

(+)-(11Z,13S,14S,15S,16S)-1-tert-Butyldimethylsiloxy-2,2,-15,16-tetrachloro-13,14-epoxy-11-tetracosene (76): The solvents were bubbled with argon for 15 min before use. To a stirred solution of (−)-**55** (134 mg, 0.481 mmol) and **71** (530 mg, 1.44 mmol) in DCE (480 μL) was added a solution of **60** (91.3 mg, 0.144 mmol) in CH_2Cl_2 (600 μL) in six portions (0, 15, 30, 45, 60, 75 min) at 35 °C while the reaction mixture was vigorously bubbled with argon (saturated with DCE).[6] After being stirred at 35 °C with argon bubbling for an additional 105 min, the reaction mixture was cooled to rt, filtered through a plug of silica gel (CH_2Cl_2, 10 mL), and concentrated in vacuo (5 mmHg). The residue was purified via column chromatography (140 mL of SiO_2, 5% CH_2Cl_2/hexanes, R_f = 0.23 in 10% CH_2Cl_2/hexanes) to give (+)-**76** (57.1 mg, 19%, >20:1 = *Z*:*E*) as a colorless oil. Data for (+)-**76**: $[\alpha]_D^{25}$ = +0.088 (*c* 2.65, $CHCl_3$); ^{1}H NMR (499 MHz, $CDCl_3$) δ 5.86 (app td, *J* = 8.9, 8.4 Hz, 1H), 5.22 (app t, *J* = 8.7 Hz, 1H), 4.29−4.24 (m, 1H), 3.92 (s, 2H), 3.82−3.77 (m, 1H), 3.65 (d, *J* = 8.9 Hz, 1H), 3.52 (dd, *J* = 8.0, 2.2 Hz, 1H), 2.22 (app q, *J* = 7.2 Hz, 2H), 2.19−2.15 (m, 2H), 1.98−1.89 (m, 1H), 1.86−1.78 (m, 1H), 1.62−1.52 (m, 3H), 1.45−1.39 (m, 3H), 1.37−1.23 (m, 18H), 0.91 (s, 9H), 0.88 (app t, *J* = 6.3 Hz, 3H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 121.6, 93.7, 72.3, 63.5, 31.3, 58.3, 54.0, 43.7, 35.9, 32.0, 29.5, 29.45, 29.43 (2C), 29.32, 29.28, 29.18, 29.12, 28.4, 26.5, 25.9, 24.9, 22.8, 18.4, 14.2, −5.2; IR (thin film) 2927, 2855, 1119, 939, 779 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{30}H_{56}O_2{}^{35}Cl_4SiNa$ [M + Na]$^+$ 639.2701, found 639.2719.

Preparation of Alkene Cross Metathesis Partner for Danicalipin A and Malhamensilipin A. ***11-Dodecenal (68):***[36] To a flask containing magnesium (3.43 g, 141 mmol) in THF (10 mL) was added 1,2-dibromoethane (275 μL, 3.19 mmol) slowly. The mixture was allowed to sit at rt until gray precipitate formed. After dilution with additional THF (70 mL), a solution of 1-bromo-10-undecene (10.0 mL, 45.6 mmol) in THF (20 mL) was added over 1 h via a syringe pump. After being stirred for 1 h, the mixture was cooled to 0 °C and allowed to settle. The liquid phase was transferred via a cannula to a rapidly stirred solution of DMF (53 mL, 684 mmol) and THF (53 mL) at 0 °C. After being stirred for 20 min at rt, the reaction mixture was diluted with hexanes (200 mL) and poured into 1 M aq HCl (200 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (200 mL × 3). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo (5 mmHg). The residue was purified by column chromatography (300 mL of SiO_2, 5% EtOAc in hexanes) to afford **68** (6.33 g, 76%) as a colorless oil. Data for **68**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.81 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.92 (dd, *J* = 10.2, 0.8 Hz, 1H), 2.41 (td, *J* = 7.6, 1.7 Hz, 2H), 2.03 (app q, *J* = 7.1 Hz, 2H), 1.62 (tt, *J* = 7.3, 6.6 Hz, 2H), 1.39−1.35 (m, 2H), 1.33−1.25 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.0, 139.2, 114.1, 43.9, 33.8, 29.4, 29.34, 29.31, 29.13, 29.07, 28.9, 22.1; IR (thin film) 2926, 2854, 2715, 1727 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{22}ONa$ [M + Na]$^+$ 205.1568, found 205.1561.

2,2-Dichloro-11-dodecenal (69):[4c] To a flask containing *t*-butylamine (634 μL, 6.03 mmol) was added 11-dodecenal (**68**) (1.00 g, 5.49 mmol) dropwise at 0 °C. After being stirred at rt for 45 min, the cloudy reaction mixture was dried over K_2CO_3 (3.79 g, 27.4 mmol), filtered, and concentrated in vacuo (25 mmHg). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 128−135 °C) to give the corresponding *t*-butylimine[4c] (1.21 g, ∼92:8 imine:aldehyde) as a colorless oil. The *t*-butylimine was dissolved in CH_2Cl_2 (15 mL), and *N*-chlorosuccinimide (2.04 g, 15.3 mmol) was added at rt under air. After being stirred for 24 h, the reaction mixture was shaken with saturated aqueous $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was diluted with hexanes, filtered, and concentrated in vacuo (25 mmHg) to give the corresponding α,α-dichloro-*t*-butylimine[4c] as a yellow oil (1.54 g, ∼94:6 dichloride:monochloride). The crude material was dissolved in THF (10 mL), and 6 M aq HCl (10 mL) was added at rt. The biphasic mixture was stirred for 2 h prior to dilution with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 2.2 cm, *l* = 7 cm, *n*-pentane/CH_2Cl_2, 2/1, R_f = ∼0.20, streaky, $KMnO_4$) and bulb-to-bulb distillation under reduced pressure (0.25 mmHg, ABT 129−135 °C) to give **69** (1.01 g, 73% over three steps, ∼94% pure) as a colorless oil. Data for **69**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.0 Hz, 1H), 2.31−2.23 (m, 2H), 2.04 (dd, *J* = 14.4, 6.9 Hz, 2H), 1.66−1.58 (m, 2H), 1.43−1.24 (m, 10H).

2,2-Dichloro-11-dodecen-1-ol (70): To a stirred solution of **69** (1.00 g, 3.98 mmol) in ethanol (12 mL) was added $NaBH_4$ (151 mg, 3.98 mmol) at 0 °C under air. After being stirred for 30 min at rt, 1 M aq HCl (12 mL) was added. The cloudy mixture was diluted with H_2O and extracted with hexanes twice. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (25 mmHg). The residue was purified by column chromatography (SiO_2, ϕ = 2.2 cm, *l* = 13 cm, *n*-pentane/CH_2Cl_2, 1/1, R_f = 0.29, *p*-anisaldehyde) to give **70** (934 mg, 93%) as a colorless oil. Data for **70**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 3.90 (d, *J* = 7.6 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 1H), 2.24−2.18 (m, 2H), 2.04 (dd, *J* = 14.3, 6.9 Hz, 2H), 1.68−1.59 (m, 2H), 1.42−1.26 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 114.2, 94.7, 72.1, 43.5, 33.8, 29.28, 29.27, 29.02, 28.98, 28.8, 24.8; IR (thin film) 3484, 2926, 2854 cm^{-1}; HRMS (CI-TOF) *m*/*z* calcd for $C_{12}H_{22}O^{35}Cl_2NH_4$ [M + NH_4]$^+$ 270.1392, found 270.1390.

12-tert-Butyldimethylsiloxy-11,11-dichloro-1-dodecene (71):[4c] To a stirred solution of **70** (348 mg, 1.37 mmol) and imidazole (187 mg, 2.75 mmol) in CH_2Cl_2 (2 mL) was added TBSCl (228 mg, 1.51 mmol) at rt. After being stirred for 48 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and shaken with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (10 mL × 3). The combined organic extracts were washed with saturated aqueous NaCl (3 mL), concentrated in vacuo (5 mmHg), and passed through a pad of silica gel (5% EtOAc in hexanes, 10 mL). The residue was purified by bulb-to-bulb distillation under reduced pressure (0.05 mmHg, ABT 170−180 °C) to afford **71** (453 mg, 90%) as a colorless oil. Data for **71**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.3, 1.7 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.92 (s, 2H), 2.15−2.19 (m, 2H), 2.04 (app q, *J* = 7.2 Hz, 2H), 1.55−1.62 (m, 2H), 1.27−1.40 (m, 10H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 114.1, 93.5, 72.1, 43.5, 33.8, 29.30, 29.29, 29.1, 29.0, 28.9, 25.7, 24.7, 18.3, −5.4; IR (thin film) 2928, 2856, 1118, 838

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cm^{-1}; HRMS (CI-TOF) m/z calcd for $C_{18}H_{36}{}^{35}Cl_2OSiNH_4$ $[M + NH_4]^+$ 384.2256, found 384.2257.

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for all new compounds and relevant chromatograms are available. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cdv@uci.edu.

Notes

The authors declare no competing financial interest.

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(31) An NMR sample of crude (±)-**27** showed no noticeable further decomposition after standing at rt overnight.

(32) Although the epoxide formation can proceed without a phase transfer catalyst, the addition of a catalytic amount of Et_4NCl facilitates the epoxide formation and ensures complete conversion.

(33) The vinyl epoxide decomposed significantly during reactions without argon bubbling.

(34) In the presence of an excess of *n*-Bu_3SnH, dechlorination of one of the *gem*-dichlorides was often observed.

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