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Catalytic Enantioselective Dihalogenation and the Selective Synthesis of (–)-Deschloromytilipin A and (–)-Danicalipin A

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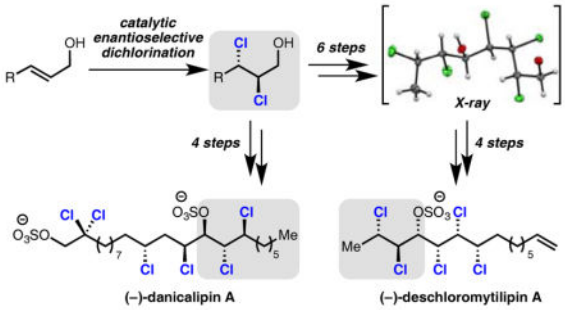
Abstract

A titanium-based catalytic enantioselective dichlorination of simple allylic alcohols is described. This dichlorination reaction provides stereoselective access to all common dichloroalcohol building blocks used in syntheses of chlorosulfolipid natural products. An enantioselective synthesis of *ent*-(–)-deschloromytilipin A and a concise, eight-step synthesis of *ent*-(–)-danicalipin A are executed and employ the dichlorination reaction as the first step. Extension of this system to enantioselective dibromination and its use in the synthesis of pentabromide stereoarrays relevant to bromosufolipids is reported. The described dichlorination and di-bromination reactions are capable of exerting diastereocontrol in complex settings allowing X-ray crystal structure analysis of natural and unnatural diastereomers of polyhalogenated stereohexads.

Graphical Abstract



1. INTRODUCTION

Although the addition of molecular chlorine to carbon–carbon double bonds is one of the oldest known organic reactions,[1a] the ability to control the enantioselectivity of alkene dichlorination has largely eluded chemists.[1b–d] Meanwhile, in recent years there has been a growing interest in the stereoselective synthesis of polychlorinated sulfolipid natural

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ASSOCIATED CONTENT
Supporting Information
Experimental procedures, characterizations, spectral data, and CIF files.
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products. Due to the scarcity of methods for enantioselective dichlorination of alkenes, syntheses of molecules within this class of natural products rely on multistep routes for establishing chlorine-bearing chiral centers in an enantioselective fashion. To date there is a single report of using an enantioselective dichlorination in the setting of complex molecule synthesis by Snyder, which employs a super-stoichiometric chiral auxiliary.[2a] A practical, catalytic, enantioselective dichlorination would be of great value to the synthetic chemist.

Slow progress in the area of enantioselective dichlorination is attributable to a number of factors. First, the highly reactive nature of most commonly employed chlorinating reagents makes achieving catalysis over nonselective background a challenge. Second, even if selectivity is achieved in the formation of an enantiopure chloronium ion (e.g. **1**, Scheme 1), regiochemical control in chloride delivery is still necessary. This is because non-regioselective chloride delivery results in a racemic product, since dichlorides formed from the two possible chloride deliveries to non-C_2-symmetric chloronium ions are enantiomers (e.g. **2** and ***ent*-2**, Scheme 1).[2b]

In 2011, Nicolaou reported the first catalytic enantioselective dichlorination of allylic alcohols.[2c] In fact, Nicolaou's dichlorination constitutes the first catalytic enantioselective *dihalogenation* of any kind.[2d–f,3] This system relies on the use of styrenyl olefins as substrates to electronically bias chloride delivery. Consequently, the selectivity of this system is poor for non-styrenyl substrates which limits its potential synthetic application and precludes its use in the synthesis of the chlorosulfolipids.

The enantioselective dichlorination of simple, alkyl disubstituted allylic alcohols has been a long sought-after transformation and would be a powerful means of entry to the chlorosulfolipids, a class of acyclic, polychlorinated natural products (Figure 1).[4] In this area, dichlorinated allylic alcohols have been identified as highly enabling intermediates in the synthesis of mytilipin A (**4**), danicalipin A (**5**), and malhamen-silipin A (**6**).[5,6] Highlighted in Figure 1 are specific dichloroalcohols that have been targeted and employed in syntheses of these molecules. Given the lack of enantioselective dichlorination methods, these motifs are either generated in racemic fashion[6a,b] or, as in the case of danicalipin A (**5**), prepared via an enriched epoxide in 4 steps and 80% ee.[6c] The allylic alcohol precursors to these dichlorides represent desirable, but challenging, settings for catalytic enantioselective dichlorinations.

Described herein is a catalytic enantioselective method for the dichlorination of simple linear aliphatic allylic alcohols. Specifically, our reported Schiff base-catalyzed dihalogenation reaction is capable of accessing the enantioenriched dichloro-alcohols involved in *all* syntheses of the chlorosulfolipids (Table 2). The utility of this method is demonstrated in a synthesis of the unnatural enantiomer of deschloromytilipin A (**3**). X-ray crystallography is used to confirm the relative configuration of the stereohexad of this natural product. The ability of this method to provide new diastereoselectivities in complex settings, as well as access to enriched polybromides, allows comparison of the conformations of natural and unnatural polychlorinated and polybrominated stereohexads in solution and solid phase. A concise eight-step synthesis of the unnatural enantiomer of danicalipin A (**5**) utilizing an enantioenriched dichloride is additionally reported.

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2. RESULTS AND DISCUSSION

2.1 Catalytic Enantioselective Dichlorination

Recently, we reported a titanium-mediated enantioselective bromochlorination of allylic alcohols catalyzed by Schiff base **11** (Table 1).[7] Trisubstituted, 1,1-disubsituted, and *cis*-disubstituted allylic alcohols were bromochlorinated under the described conditions with excellent regio- and enantioselectivity. Unfortunately, application of this system to disubstituted *trans*-allylic alcohol **9** provided bromochloride **10a** and its corresponding bromochloride constituational isomer in a 1.7 to 1.0 ratio, respectively. Reduced temperatures provided a slight improvement in bromochloride product rations (3.0:1.0, Table 1, entry 2). As depicted in Scheme 1, one would expect that if a 1.7 to 1.0 or a 3.o to 1.0 product ratio persisted for the case of di-chlorination, the enantioselectivity of dichloride products would be limited to a modest 26% or 50% ee, respectively, assuming the intermediacy of a discrete enantioenriched chloronium ion.

The viability of a selective dichlorination of *trans*-disubstituted allylic alcohols was initially investigated by replacing *N*-bromosuccinimide (NBS) with *N*-chlorosuccinimide (NCS) as a source of electrophilic chlorine in our titanium-mediated dihalogention reaction (Table 1, entry 3). This provided dichloride product **10b** in fair yield and higher-than-predicted enantioselectivity (i.e. greater than 26% ee). Such enantioselectivity could originate from an increased regioselectivity in chloride delivery in the case of trapping chloronium intermediates by chlorotitanium species. Another possible explanation is that diastereomeric chloronium-containing titanium complexes are attacked by chloride with different regioselectivity.

Subsequent investigation revealed *tert*-butylhypochlorite (*t*-BuOCl) as the most selective source of electrophilic chlorine (Table 1, entries 4–8). This is surprising given the highly reactive nature of *t*-BuOCl, which exhibits substantial background reactivity in the absence of a chiral catalyst. Mechanistically, we speculate that a chiral titanium complex acts as an oxophilic Lewis acid on *t*-BuOCl, accelerating transfer of the electrophilic chlorine to the olefin of the titanium-bound allylic alcohol. The higher selectivity for dichlorinations with *t*-BuOCl compared with NCS could arise from the closer proximity of the oxygen and chlorine in *t*-BuOCl, situating the chlorine nearer the chiral ligand which is presumably also titanium-bound. Use of ligands other than chiral iminodiol **11** or solvents other than hexanes resulted in diminished selectivity (Table 1, entries 9–11). Decreased temperatures improved both the yield of and selectivity for dichloride **10b** and permitted reduction in catalyst loading (Table 1, entries 12–13). Further improvements in selectivity were observed in larger scale reactions employing more controlled drop-wise additions of *t*-BuOCl solutions.

As a benchmark substrate, cinnamyl alcohol **16** was subjected to the dichlorination conditions and produced dichloride (+)-**17** in excellent yield and selectivity (Table 2, entry 1). Previously, enantioenriched (+)-**17** and (–)-**17** were prepared by Nicolaou in +61% and –81% ee, respectively, using 20 mol % pseudoenantiomeric $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$.[2c]

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Linear, aliphatic allylic dichloroalcohols **19**, **21**, and **23** are enantioenriched versions of intermediates that have been used in syntheses of mytilipin A, danicalipin A, and malhamensilipin A, respectively (Table 2, entries 2–4).[6a–c] Dichlorination of allylic alcohols **18, 20,** and **22** under our developed conditions produced the aforementioned dichloroalcohols on practical scale and in synthetically useful yields and enantioselectivities. The low yield in the dichlorination of **18** is likely due to the volatility of dichloride **19**, which is isolated via distillation. Dichloroalcohol **21**, which is used in our synthesis of *ent*-(–)-danicalipin A (–)-**5** (see Section 2.6), was prepared on 9.1 gram-scale in a single run. The skipped diene **24** presents an interesting chemoselectivity challenge and contains allylic protons which could be acidic within a chloronium intermediate. Our system can dichlorinate the more electron-deficient olefin of **24** to produce **25** in fair yield and good enantioselectivity (Table 2, entry 5); compound **25** maps on to nominal undecachlorosulfolipid **7** (Figure 1). As previously reported, our conditions can dihalogenate 1,1-disubstituted allylic alcohol **26** to furnish **27** selectively (Table 2, entry 6).[7] Trisubstituted allylic alcohols are converted to dichlorides with low yield using this method due to facile deprotonation of trisubstituted chloronium ions to give allylic chloride products.

2.2 Catalytic Enantioselective Dibromination

Endeavors to extend our system for dichlorination to the dibromination of allylic alcohols was next undertaken. Like dichlorination, alkene dibromination has been a longstanding challenge in the area of enantioselective catalysis. From a practical perspective, enantioenriched dibromides could have great value as stereodefined building blocks for further functionalization. A palladium-catalyzed enantioselective alkene dibromination was reported in 2003 by Henry,[3a] but a subsequent report by Denmark[3b] questioned these results. In their reinvestigation, all attempts to reproduce this chemistry returned racemic dibromides. In 2013 our lab reported a TADDOL-catalyzed enantioselective dibromination reaction which was enantioselective only for electronically biased cinnamyl alcohols.[2d] We envisioned that our success in the enantioselective dichlorination of simple allylic alcohols could translate back to enantioselective dibromination.

When NBS and $BrTi(O\textit{i}\text{-}Pr)_3$ were used in place of *t*-BuOCl and $ClTi(O\textit{i}\text{-}Pr)_3$ in the halogenation reaction, dibromides were formed in high yield and selectivity (Table 3). As in the case of dichlorination, the origins of this higher-than-predicted selectivity are unclear; possible explanations parallel those discussed earlier for dichlorination (Section 2.1).

Dibromination of electronically biased allylic alcohol **16** proceeded smoothly, providing **28** in good yield and selectivity[2d] (Table 3, entry 1). Electronically unbiased allylic alcohols **18**, **20**, and **22** were also selectively dibrominated providing **29**, **30**, and **31** in good yields (Table 3, entries 2–4). 1,1-Disubstituted olefins such as **26** could be brominated as well, producing **32** efficiently and with good selectivity (Table 3, entry 5). In contrast to dichlorination, trisubstituted allylic alcohols are also viable substrates for di bromination.[7] It is anticipated that these enriched dibromides could serve as useful chiral building blocks.

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2.3 Synthesis of (–)-Deschloromytilipin A

With >10 grams of enantioenriched **19**, a synthesis of the enantiomer of natural product (+)-(**3**), herein refered to as deschloromytilipin A, was executed (Scheme 2). This chlorosulfolipid was isolated in 2010[4e] and lacks the vinyl choride found in mytilipin A. Using a strategy similar to that of Yoshimitsu[6c] and Vanderwal,[6a,b] oxidation and chloroallylation[8] of **19** provided known trichloroalcohol **34** as a single diastereomer. Although never previously elaborated to a chlorosulfolipid, alcohol **34** has been prepared from crotyl alcohol in five chemical transformations in 66% ee using a kinetic resolution.[6a,b] Acryloylation of **34** and subsequent ring-closing metathesis yielded lactone **35**, which was then reduced[9] to enediol **36**. The application of a *Z*-selective cross metathesis between 1,4-butenediol and chlorohydrin **34** to directly prepare diol **36** was attempted, but no reaction was observed.[6a,10] In the course of this synthesis, it was found that diol **36** is prone to undergo facile intramolecular cyclization via an S_N2' displacement of the allylic chloride by the secondary alcohol. Hence, **36** was used directly after preparation to prevent this unwanted decomposition. Dichlorination of **36** with Et_4NCl_3[11] furnished diol **37** with high diastereoselectivity. Silylation and triflation of **37** provided pentachloride **38**. Copper-catalyzed alkyl–alkyl cross coupling[12] of **38** followed by sulfation completed the first synthesis of (–)-deschloromytilipin A (–)-**3** in 11 steps from crotyl alcohol. This route provides access to the unnatural enantiomer of the natural product, which was targeted in order to demonstrate the power and utility of enantioselective catalysis when both ligand antipodes are readily available. This work also represents the first use of an enantioselective dihalogenation in the synthesis of a chlorosulfolipid.[13]

2.4 Synthesis of a Polybrominated Precursor Relevant to Bromosulfolipids

When the danicalipin A-producing organism, *O. danica*, is grown in bromide-rich media, the corresponding bromosulfolipid is purportedly made.[14a] This curiosity raises questions about the pathways and molecular machinery responsible for halogenation in these phytoflagellates, as well as fundamental structural questions about these bromosulfolipids. The salient barrier to the study of these peculiar molecules is the limited data that exists for their characterization. Indeed, isolation reports for most bromosulfolipids identify these structures solely by mass spectrometry.[14] Prompted by a desire to provide structural and characterization data for relevant polybrominated motifs, selective syntheses of such stereoarrays were carried out.[6k]

The synthesis of the olefin precursor to pentabromodiols proceeded in an analogous manner to the synthesis of **36** (Scheme 3). Oxidation of enantioenriched dibromide **29** provided dibromoaldehyde **39**, which was particularly capricious relative to its dichloroaldehyde counterpart and rapidly eliminated HBr upon standing at room temperature. Dibromoaldehyde **39**, however, could be combined immediately with preformed bromoaluminum reagent **40**[6a,b,15] to provide multigram quantaties of bromohydrin **41**. Allylic bromide **41** could be further elaborated by acroylation and ring closing metathesis to provide lactone **42**. Cerium borohydride reduction[9] afforded diol **43** on gram scale. The relatively high efficiencies of these transformations were surprising given the generally perceived sensitivity of allylic bromide, dibromide, and bromohydrin functionalities.[6k]

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2.5 Synthesis and Solid State Conformation of Polychloride and Polybromide Stereohexads

Characterization and conformational data on stereohexad structures of type **37** and its polybrominated analogues could prove practically useful and academically insightful. First, synthesis and characterization of polybromide stereohexads would help confirm the existence of putative bromosulfolipids.[6k] Second, conformational data on **37** could provide insight in to the manner in which these molecules assemble in a lipid membrane. Third, investigation of unnatural diastereomers of **37** would expand the repertoire of characterization data for complex polyhalostereoarrays. This could be particularly useful in the stereochemical characterization of molecules like nominal undecachlorosulfolipid **7**. For these reasons the syntheses of chlorinated and brominated stereohexads was undertaken.

With pentachloride **37** already made, the completion of the synthesis of the analogous pentabromide was conducted (Scheme 4). This was effected through a diastereoselective dibromination of alkene **43** with pyridinium tribromide and resulted in the predominant formation of a stereohexad with the same relative configuration as pentachloride **37**. Such diastereoselectivity in dihalogenation of **36** and **43** using trihalide reagents is in accordance with previous reports concerning the dichlorination of similar substrates.[6a,b,h] The high diastereoselectivity (18:1) observed in the dichlorination suggests that strong substrate bias exists for the halogenation of substrates of this type.

Efforts were made to obtain X-ray quality crystals of stereohexad **37** and its brominated analogue to compare the conformations of these polyhalides in the solid state. This presented a clear challenge due to the non-crystalline nature of such lipids. After intensive efforts, it was found that ferrocene carboxylate esters **44** and **46** were crystalline solids. Interestingly, **44** and **46** possess a “bent” conformation in the solid state (Scheme 4, top). This conformation is in agreement with that previously predicted by computation and observed in NMR studies for **3**.[4k] Conversion of **37** to (–)-deschloromytilipin A (–)-**3** (Scheme 2) confirms its absolute and relative configuration. This represents a unique case wherein the absolute and relative configuration of the complete stereoarray within a chlorosulfolipid natural product has been confirmed by X-ray crystallography.[16]

During our studies on polyhalogenated stereohexads, it was found that our reported catalytic system can overturn inherent substrate bias to provide access to unnatural diastereomers (**36** to **45**, and **43** to **47**, Scheme 4). This selectivity is particularly impressive considering the number of halogen atoms that could participate in anchimeric assistance.[17] Treating tribromoenediol **43** with the titanium-based dihalogenation conditions in the absence of ligand resulted in a reversal of inherent diastereoselectivity to 1:6 favoring diastereomer **47**. Interestingly, the use of ligand (*S,R*)-**11** resulted in the formation of **47** as the major diastereomer but in a lower diastereomeric ratio (2.3:1). On the other hand, the use of ligand enantiomer (*R,S*)-**11** resulted in the formation of **47** with higher diastereoselectivity (11:1 dr). This suggests a matched/mismatched diastereoselectivity scenario between the ligand and the titanium-bound substrate – the inherent selectivity of titanium-based dibromination favors diastereomer **47**, which is either enhanced or counteracted by the appropriate chiral ligand. Application of our dichlorination conditions to **36** with matched ligand enantiomer

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(*R,S*)-**11** provided selective access to unnatural **45** in >20:1 dr. Prior to this work, there was no way to overturn the inherent diastereoselectivity of a given substrate in a dihalogenation without changing the substrate itself.

These unnatural polychloride and polybromide stereohexads could be crystallized as their *p*-bromobenzoates, **45** and **47**. In contrast to the natural diastereomers, **45** and **47** possess a linear conformation in the solid state (Scheme 4, bottom). The implications of the structural differences between these polyhalide diastereomers for biological systems are intriguing but at this point unclear. Both pairs of crystal structures for the same diastereomers of pentachlorides and pentabromides (i.e. **44** and **46**, and **45** and **47**, Scheme 4) show remarkable conformational similarity at the unit cell level. This is unexpected given the differences in Van der Waals radii, polarizability, C–X bond length and electronegativity between chlorine and bromine.[18] Pentachlorides **44** and **45** also provide characterization data for unnatural diastereomers of the stereohexad contained within the putatively assigned stereooctad of undecachlorosulfolipid **7**.[6h,i]

2.6 Synthesis of (–)-Danicalipin A

The chlorosulfolipid danicalipin A (**5**) is estimated to comprise >90% of all polar lipids in the flagellar membrane of freshwater *Ochromonas danica* algae.[19] It possesses a unique structure for a lipid,[4b] containing two anionic sulfate moieties, one at the terminus and one near the center of its otherwise hydrophobic linear core. Owing to this unusual structural feature and its complex halogenation pattern, danicalipin A has attracted much synthetic interest. To date there have been five reported syntheses of danicalipin A, the most efficient of which are 9 and 12 linear steps by Vanderwal[6a] and Carreira,[6j] respectively. Both of these syntheses commence from allylic alcohol starting materials. In the Vanderwal synthesis, access to an enantioenriched dichlorinated intermediate is achieved via a racemic dichlorination followed by resolution of a later intermediate. In the Carreira synthesis, the vicinal dichloride motif is established through diastereoselective epoxidation followed by chlorinolysis of the epoxide. We envisioned that our chemistry could be used to streamline the synthesis of danicalipin by providing one-step, enantioselecitve access to the requisite dichloride building block **21**.

Strategically, it was thought that the unnatural enantiomer of danicalipin A might be prepared through a formal hydrochlorination of *trans* alkene **48**, followed by sulfation (Scheme 5). Enantioenriched chlorohydrin alkene **48** might then be synthesized through an enantioselective chloroallylation reaction involving enantioenriched dichloroaldehyde **49** and a discrete, enantiopure chloroallylboronate of general structure **50**. Aldehyde **49** would arise from dichlorination and oxidation of allylic alcohol **20**. It was surmised that highly functionalized chloroallylboronate **50** might be prepared stereoselectively from a (*Z*)-chlorovinylboron reagent **51** and organometallic species **52** and **53** via the homologation chemistry of Matteson.[20]

The forward synthesis commenced with the development of a scalable synthesis of an appropriate (*Z*)-chlorovinylboron reagent (Scheme 6). The preparation of an analogous (*Z*)-(2-bromovinyl)-MIDA boronate has been accomplished previously by Burke.[21] Following a

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similar strategy it was found that (*Z*)-(2-chlorovinyl)-MIDA boronate could be synthesized efficiently in one step by treatment of commercially available **54** with iodine monochloride in the presence of 2,6-lutidine. The pure product could be easily isolated by precipitation from diethyl ether. Subsequent treatment with aqueous hydroxide in the presence of one equivalent of commercial enantiopure diol **55** provided chromatographically stable chlorovinylboronic ester **56**.[20a]

Homologation to 1,3-dichloroallyl boronic ester **57** was next accomplished by treatment of **56** with dichloromethyllithium followed by zinc chloride according to Matteson's procedure.[20b,c] Boronic ester **57** was unstable to chromatographic purification and prolonged storage, but solutions of crude **57** could be advanced to fully functionalized chloroallyl boronic ester **58** via a reaction involving the Grignard reagent of alkyl iodide **59**. Boronic ester **58** was of >99% ee as determined by Mosher analysis after oxidation of **58** to its corresponding alcohol. This selectivity is particularly impressive as α-chloroallyl boronic esters have a high propensity to epimerize and decompose.[20a,d] Addition of magnesium bromide diethyl etherate to the organolithiate was crucial, as solutions of the intermediate organolithiate were found to be unstable and rapidly undergo lithium-halogen exchange on the gem-dichloride moiety.

With chloroallyl boronic ester **58** in hand, allylation reactions were attempted with aldehyde **49** which was obtained through oxidation of enantioenriched dichloroalcohol (–)-**21**. Initial attempts were low yielding and required excess dichloroaldehyde due to its propensity to decompose under the reaction conditions. Gratifyingly, it was found that chloroallyl boronic ester **58** could be induced to react efficiently with aldehyde **49** at low temperature by first activating it *in situ* as the borinate. This was accomplished through the addition of *n*-butyllithium and trifluoroacetic anhydride following a procedure developed by Aggarwal.[22] Accordingly, this reaction afforded gram-quantaties of chlorohydrin alkene **60** as a *single enantio- and diastereomer* in 75% yield. Serendipitously, it was discovered that a kinetic resolution occurs during this chloroallylation reaction, with the minor enantiomer of dichloroaldehyde **49** being essentially unreactive.

After failed attempts to directly hydrochlorinate **60**,[23] a formal hydrochlorination was achieved through a bromochlorination–radical debromination sequence.[24] Initial attempts to bromochlorinate **60** provided the desired bromochloride in low yield due to competitive bromoetherification arising from capture of an intermediate bromonium by the secondary alcohol of **60**. Investigation of bromochlorination conditions identified $Me_4N(Cl_2Br)$[25] as the best source of "BrCl," providing the desired bromochloride **63** in a mere 21% yield along with 65% yield of bromoether **64**, both as single diastereomers (Scheme 7). Although low yielding, the clean reactivity was encouraging as previous reports concerning the iodochlorination of similar substrates gave complex mixtures of products.[6a] Protection of the alcohol in **60** completely shut down any desired reactivity and underscored the need for having a free alcohol for this dihalogenation reaction. This led us to hypothesize that the ratio of desired bromochloride to undesired bromoether might be influenced by *O*-deuteration of **60** as this should alter the nature of hydrogen bonding between substrate and halogenating agent. In practice it was found that pretreatment of alcohol **60** with methanol-

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d_4 followed by solvent removal and subsequent reaction with $Me_4N(Cl_2Br)$ in acetonitrile increased the yield of the bromochlorination to 44%.[26]

Rationale for this observed change in product ratio is depicted in Scheme 7. Based on the subsequent transformation of bromochloride **63** to (–)-danicalipin A (–)-**5** (Scheme 6) and NOE analysis of bromoether **64** (see Supporting Information), it was determined that these products likely arise from diastereomeric bromonium intermediates **61** and **62**. Assuming bromonium formation occurs on the conformer for **60** displayed in Scheme 7, the *undesired* bromonium formation could be directed through hydrogen bonding of the secondary alcohol; deuteration may then render this direction less effective, thus reducing the amount of bromoether. Another possible rationalization is that bromonium formation is reversible and deprotonation of the alcohol during bromoetherification is selectivity determining. Accordingly, the stronger oxygen-deuterium bond would be harder to heterolytically cleave, effectively disfavoring the bromoetherification pathway.

Our synthesis of the unnatural enantiomer of danicalipin A was completed by radical debromination of **63** followed by sulfation (Scheme 6). It is noteworthy that radical debromination can be carried out chemoselectively (74% yield based on recovered starting material) in the presence of alkyl chloride and geminal dichloride functionalities. The described synthesis is 8 linear steps and provides access to a single isomer of (–)-danicalipin A (–)-**5**.

3. CONCLUSION

The enantioselective dichlorination and dibromination of electronically unbiased, aliphatic allylic alcohols has been demonstrated. The developed method is practical, scalable, and provides access to valuable dichloroalcohols used in the preparation of chlorosulfolipid natural products. Enantioselective syntheses of two chlorosulfolipids, *ent*-(–)-deschloromytilipin (–)-**3** and *ent*-(–)-danicalipin A (–)-**5**, using this chemistry as the first step has been described, highlighting the utility and practicality of the system. We anticipate that this method could enable the selective syntheses of all members of the chlorosulfolipid family. Conversion of the dihalo-alcohol products to the relevant stereoarry of naturally occurring stereohexads has provided insight into the absolute stereochemistry of these molecules as well as their conformation. The tactics reported here may be applied to both the synthesis and structural assignment of undecachlorosulfolipid **7** whose structure remains ambiguous.[6h,i]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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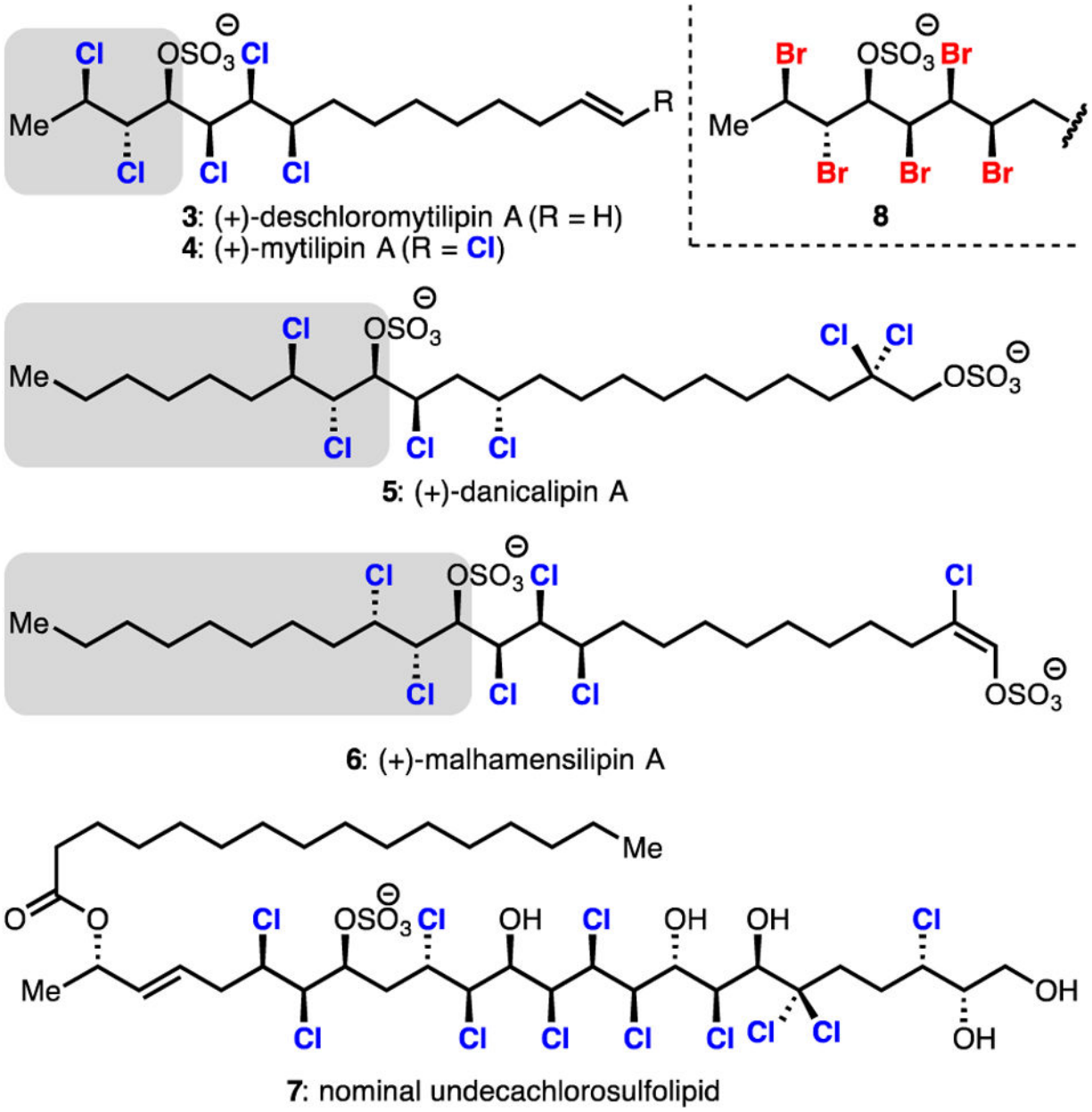
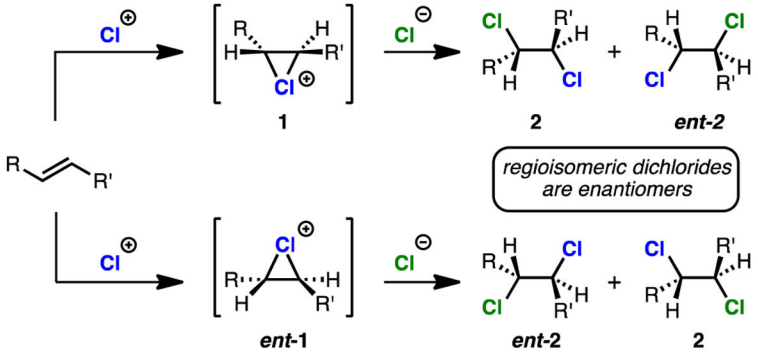


Figure 1.

Structures of chlorosulolipid natural products (**3**–**7**) and an analogous bromosulfolipid stereohexad (**8**). Highlighted structures represent corresponding simple dichlorinated allylic alcohols that have been targeted in synthesis.



Scheme 1.

A challenge in enantioselective dichlorination.

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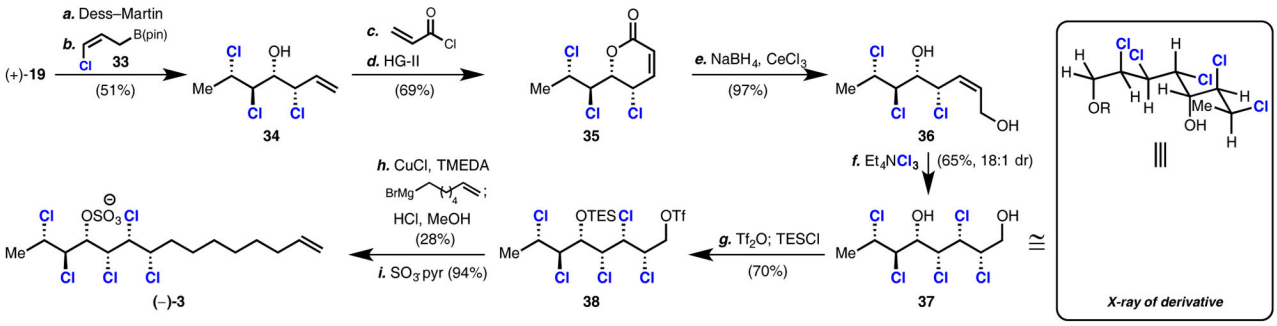

Scheme 2. Synthesis of (–)-Deschloromytilipin A[a]

[a]Reagents and conditions: (a) Dess–Martin periodinane (1.3 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 0 °C; (b) (*Z*)-chloroallylpinacolborinate **33** (1.0 equiv), *n*-BuLi (1.2 equiv), trifluoroacetic anhydride (1.3 equiv), THF, −78 °C, 51% over two steps; (c) acryloyl chloride (2.0 equiv), *i*-Pr_2NEt (1.8 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0 °C, 80%; (d) Hoveyda–Grubbs II (2 mol %), toluene, 90 °C, 86%; (e) $CeCl_3{\cdot}7H_2O$ (2.4 equiv), $NaBH_4$ (2.4 equiv), EtOH, rt, 97%; (f) Et_4NCl_3 (1.o equiv), 10:1 CH_2Cl_2/EtOH, −78 °C, 65% (18:1 dr); (g) Tf_2O (1.2 equiv), 2,6-lutidine (1.2 equiv), CH_2Cl_2, 0 °C, 82%; TESOTf (1.7 equiv), 2,6-di-*tert*-butylpyridine (1.7 equiv), CH_2Cl_2, 0 °C, 85%; (h) CuCl (0.1 equiv.), *N,N,N′,N′*-tetramethylethylenediamine (0.3 equiv), 6-hepten-1-yl magnesium bromide (1.2 equiv), THF, 0 °C to rt; 1 M aq. HCl, MeOH, rt, 28%; (i) $SO_3{\cdot}$pyridine (3.o equiv), THF, rt, 94%.

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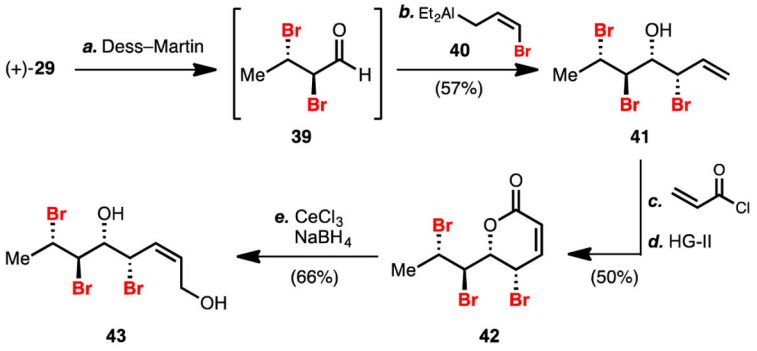
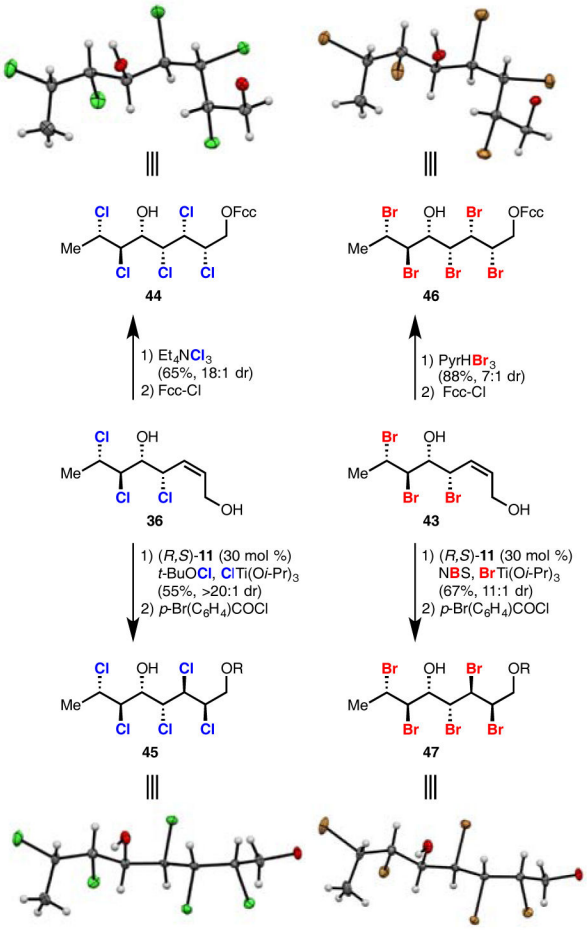


Scheme 3. Synthesis of Stereotetrad 43[a]

[a]Reagents and conditions: (a) Dess–Martin periodinane (1.3 equiv.), NaHCO3 (3.0 equiv.), CH_2Cl_2, 0 °C; (b) 2,2,6,6-tetramethylpiperidine (2.2 equiv.), *n*-BuLi (2.1 equiv.), allyl bromide (2.1 equiv.), $AlEt_2Cl$ (4.0 equiv.), THF, −78 °C, 57%; (c) acryloyl chloride (1.5 equiv.), *i*-Pr_2NEt (1.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 0 °C, 61%; (d) HG-II (2.5 mol %), toluene, 90 °C, 82%; (e) $CeCl_3{\cdot}7H_2O$ (2.4 equiv.), $NaBH_4$ (2.4 equiv.), EtOH, 0 °C, 66%.



Scheme 4. Synthesis of Stereohexads 44–47[a]

[a]X-ray crystal structures of the natural and unnatural diastereomers of the polychloride stereohexad found within mytilipin A, along with their polybrominated analogues. The aryl carboxylate esters have been omitted in the crystal structures for clarity. Fcc = ferrocene carboxylate and R = *p*-bromobenzoate.

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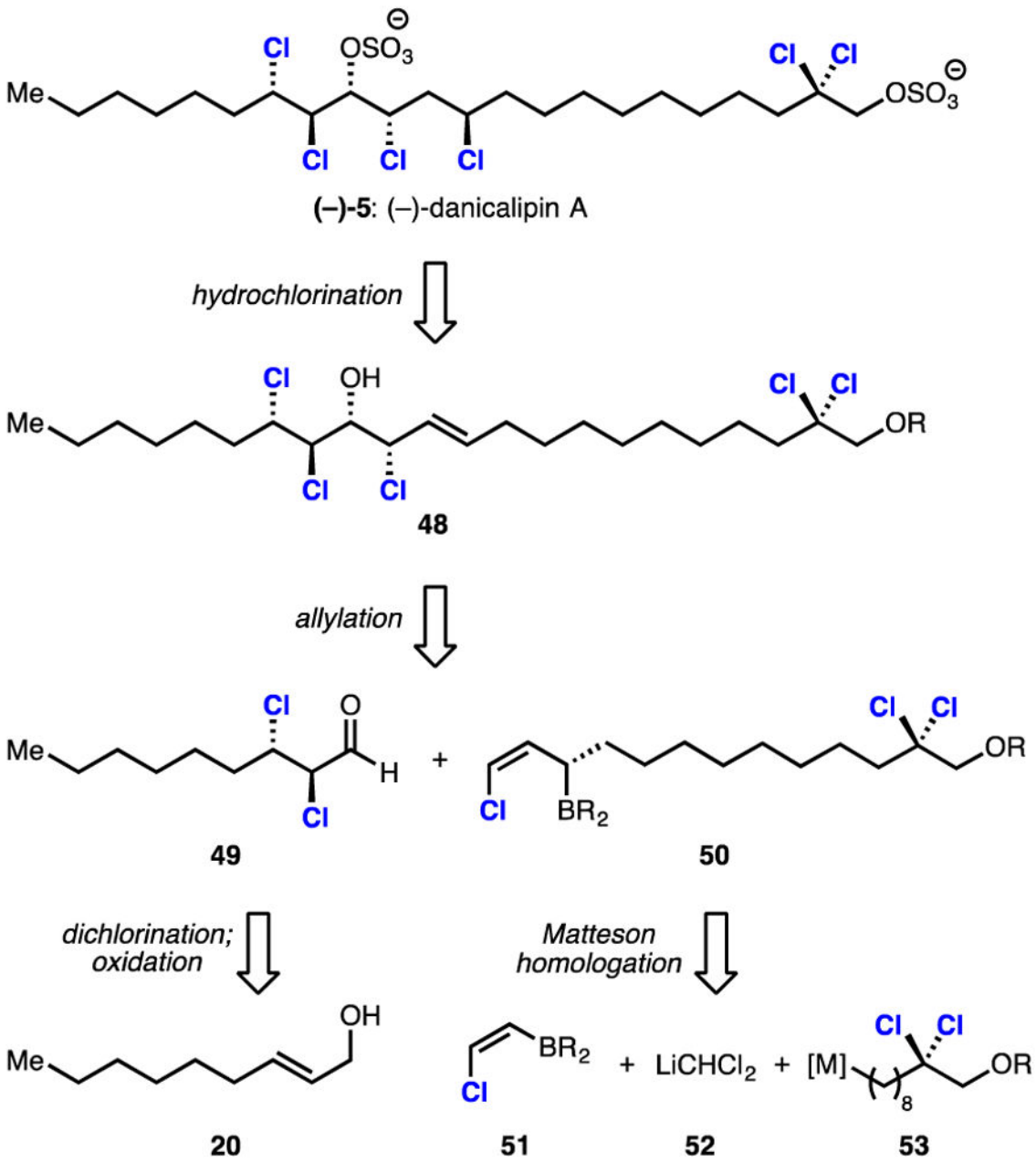
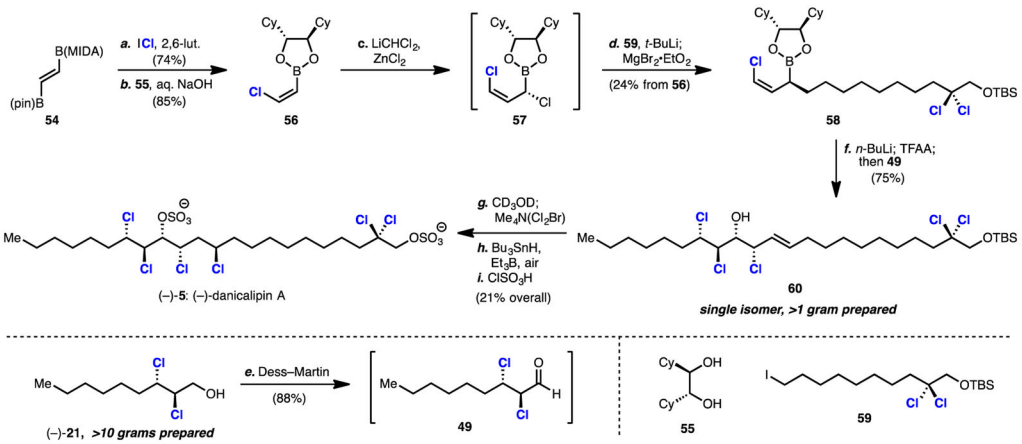


Scheme 5.
Retrosynthesis of (–)-Danicalipin A



Scheme 6.

Concise Synthesis of (–)-Danicalipin A[a]

[a]Reagents and conditions: (a) iodine monochloride (2.0 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C to rt, 74%; (b) (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol **55** (1.1 equiv), aq. NaOH, THF, 0 °C, 85%; (c) CH_2Cl_2 (1.5 equiv), *n*-butyllithium (1.1 equiv), THF, –100 °C; **56**, $ZnCl_2$ (1.0 equiv), –100 °C to rt; (d) **59** (1.0 equiv), *t*-butyllithium (1.1 equiv), Et_2O/hexanes, –78 °C; magnesium bromide ethyl etherate (1.2 equiv); then **57** (1.1 equiv), THF, –78 °C to rt, 24% from **56**; (e) Dess–Martin periodinane (1.3 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 0 °C to rt, 88%; (f) *n*-butyllithium (1.9 equiv), trifluoroacetic anhydride (1.9 equiv), THF, –78 °C; **49** (1.1 equiv), –78 °C to rt, 75% (g) methanol-d_4, rt; concentrate; tetramethylammonium dichlorobromate (1.1 equiv), CH_3CN, rt; (h) tributyltin hydride (1.1 equiv), triethylborane (0.2 equiv), air, toluene, –78 °C, 22% over two steps; (i) chlorosulfonic acid, CH_2Cl_2, rt, 93%.

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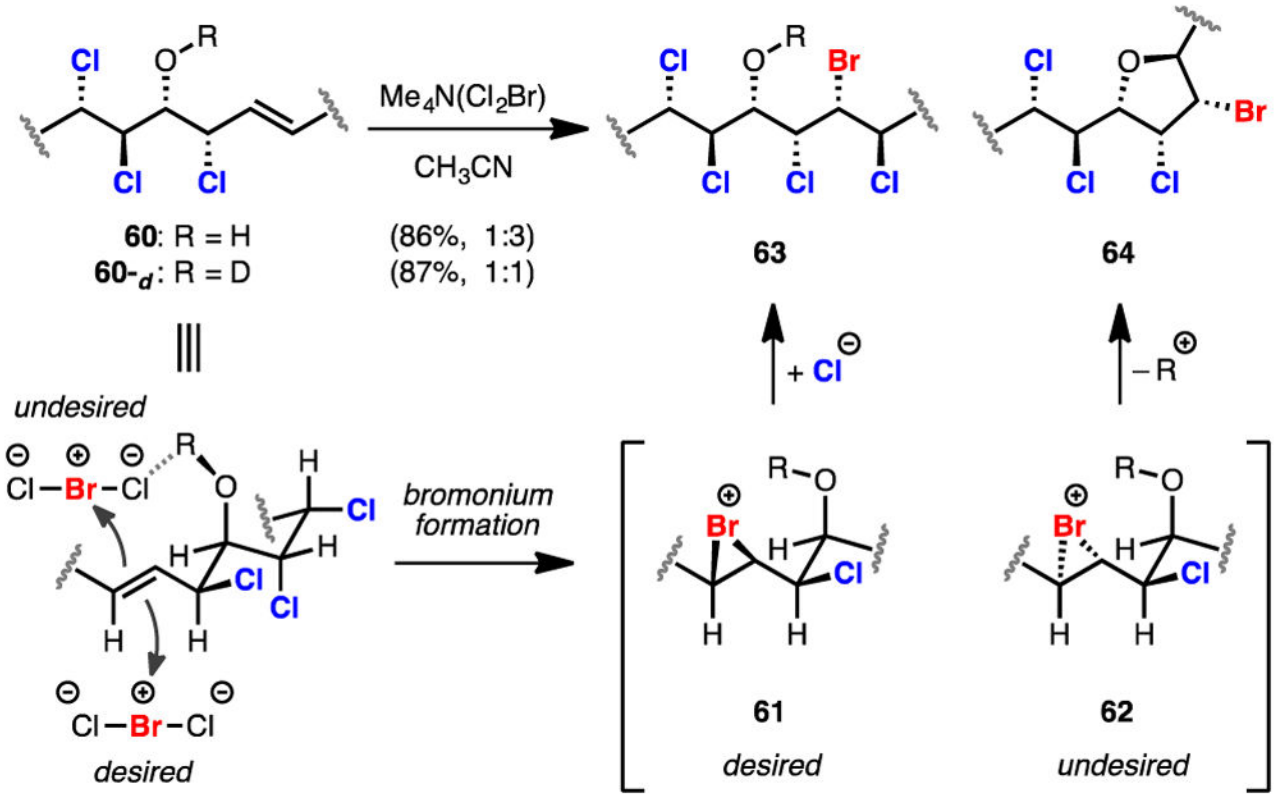

Scheme 7.
Rationale for the Effect of *O*-Deuteration

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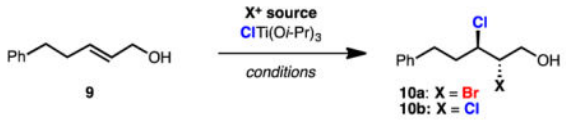
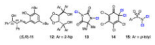
Table 1

Development of an Enantioselective Dichlorination of Allylic Alcohols[a]



entry	X^+ source	*conditions*	yield (%)	ee (%)
1	NBS	30 mol% **11**, hexanes, r.t.	90	66 (1.7 : 1.0)[b]
2	NBS	30 mol% **11**, hexanes, −20 °C	81	90 (3.0 : 1.0)[b]
3	NCS	30 mol% **11**, hexanes, r.t.	52	62
4	**13**	30 mol% **11**, hexanes, r.t.	70	65
5	$PhICl_2$	30 mol% **11**, hexanes, r.t.	12	6
6	**14**	30 mol% **11**, hexanes, r.t.	*trace*	–
7	**15**	30 mol% **11**, hexanes, r.t.	66	58
8	*t*-BuOCl	30 mol% **11**, hexanes, r.t.	56	72
9	*t*-BuOCl	30 mol% **12**, hexanes, r.t.	73	5
10	*t*-BuOCl	30 mol% **11**, CH_2Cl_2, r.t.	62	20
11	*t*-BuOCl	30 mol% **11**, Et_2O, r.t.	75	67
12	*t*-BuOCl	30 mol% **11**, hexanes, −20 °C	77	78
13	*t*-BuOCl	10 mol% **11**, hexanes, −20 °C	82	76



[a]Reactions were conducted on 0.1 mmol scale with 1.1 equiv X^+ source and 1.1 equiv ClTi(O*i*-Pr)3. Yields were assessed by ^{1}H-NMR spectroscopy with 1,4-dinitrobenzene as an internal standard;

[b]Ratio of bromochloride constitutional isomers. Yields given for entries 1 and 2 are for both constitutional isomers and ee is reported for the major isomer.

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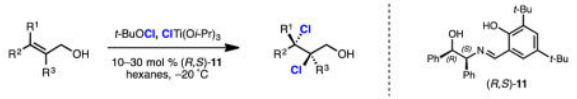
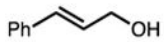
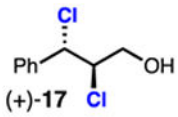
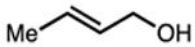
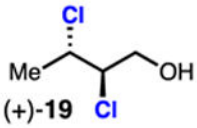
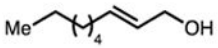
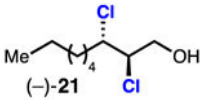
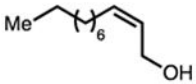
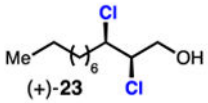
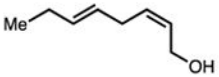
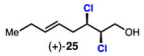
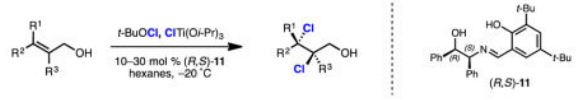
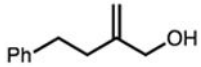
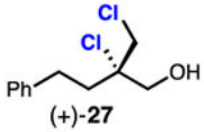
Table 2

Dichlorination Substrate Scope[a]



entry	*substrate*	yield (%)	ee (%)	mol % 11	*product*	*prior art or use in synthesis*
1[b]	 **16**	83	91	10	 (+)-**17**	*Nicolaou* (2011): 58%, +61% *ee* $ArlCl_2$, 20 mol % $(DHQD)_2PHAL$
2	 **18**	64[c]	80	15	 (+)-**19**	**(deschloro)mytilipin A** *Vanderwal* (2013): (±)-**19** *Burns* (this work): (+)-**19**
3	 **20**	86	83	15	 (–)-**21**	**danicalipin A** *Yoshimitsu* (2011): (+)-21 *Vanderwal* (2014): (±)-**21** *Burns* (this work): (–)-**21**
4[d]	 **22**	64	81	20	 (+)-**23**	**malhamensilipin A** *Vanderwal* (2014): (±)-**23**
5[d]	 **24**	45	85	30	 (+)-**25**	**nominal undecachlorosufolipid** (yet to be utilized)



entry	substrate	yield (%)	ee (%)	mol % 11	product	prior art or use in synthesis
6[d]	 **26**	61	90	30	 (+)-**27**	*Burns* (*2015*)

[a]Conditions unless otherwise noted: 1.1–1.5 equiv *t*-BuOCl, 1.1–1.6 equiv ClTi(O*i*-Pr)$_3$, 10–30 mol % (*R,S*)-**11**, hexanes, −20 °C, 4–12 hours;

[b]3:1 hexanes/CCl_4;

[c]isolated by distillation;

[d]absolute configuration unconfirmed.

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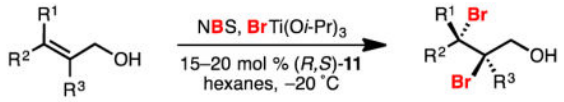
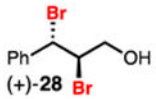
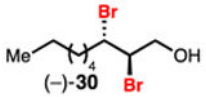
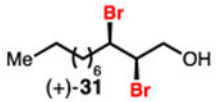
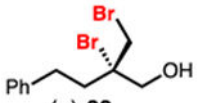
Table 3

Dibromination Substrate Scope[a]



entry	*substrate*	*product*	yield (%)	ee (%)	mol % 11
1[b]	**16**	 (+)-**28**	75	87	15
2	**18**	(+)-**29**	82	80	20
3[c]	**20**	 (–)-**30**	86	80	15
4[c]	**22**	 (+)-**31**	79	86	20
5[c]	**26**	 (+)-**32**	84	81	20

[a]Conditions unless otherwise noted: 1.1 1.2 equiv NBS, 1.1 1.3 equiv BrTi(O*i*-Pr)3, 15–20 mol % (*R,S*)-**11**, hexanes, −20 °C, 4–12 hours;

[b]3:1 hexanes/CCl_4;

[c] absolute configuration unconfirmed.

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