Recent progress toward synthesis of chlorosulfolipids: total synthesis and methodology

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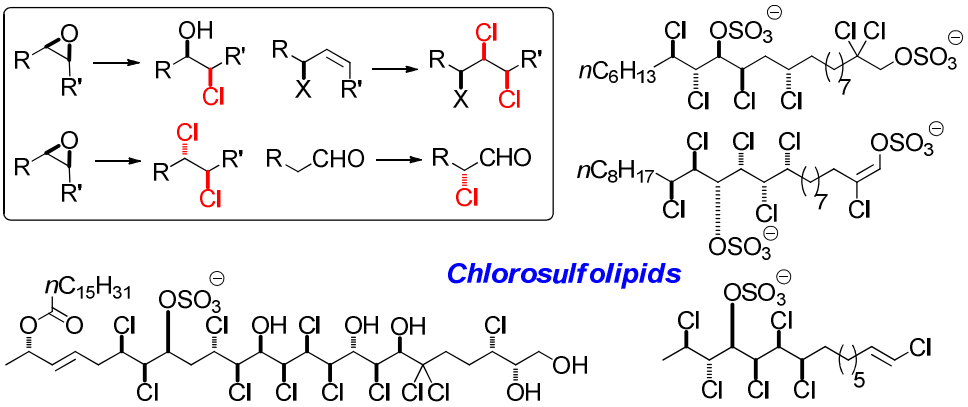
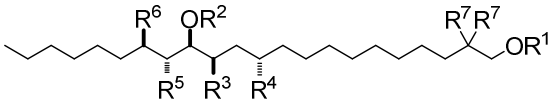
Abstract

Chlorosulfolipids (CSLs) are an intriguing family of natural products featuring highly chlorinated linear hydrocarbon skeletons. Although CSLs were first isolated in 1962, chemical synthesis of CSLs was hampered because relevant methods for stereoselective construction of the polychlorinated motifs of CSLs were scarce. Since Carreira's first total synthesis of the CSL mytilipin A in 2009, several groups, including our own, have reported total syntheses of CSLs. As a result of these total syntheses, important progress has been made in the development of reliable synthetic methods for stereoselective polychlorination. In this digest, we summarize the total syntheses of CSLs by focusing on synthetic methods for stereoselective polychlorination of the organic frameworks of CSLs.

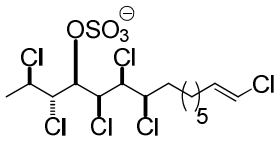


Introduction

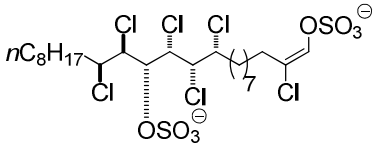
Chlorosulfolipids (CSLs), first isolated from *Ochromonas danica* by Haines in 1962,[1a] are an unusual family of chlorine-rich lipids which includes danicalipin A (**1**), mytilipins A-C (**7**, **9**, and **10**), and malhamensilipin A (**8**) (Figure 1).[1] CSLs are unique in featuring hydrocarbon skeletons densely functionalized with chlorine atoms. Around 1970, studies concerning producers,[2] biological activities,[3] and biosyntheses of CSLs[4] were reported. For example, *O. danica* and *Poterioochromonas malhamensis* were identified as producers and toxicity against fish and invertebrates,[3a,3b] growth inhibition of bacteria,[3c,3d] and lysis of mammalian erythrocytes[3e-g] were revealed. After further investigations throughout the 1970s, research on CSLs largely subsided owing to the lack of availability of CSLs from natural resources and chemical access to CSLs.



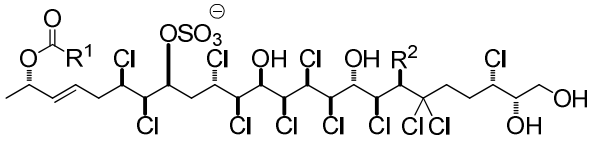
	R^1	R^2	R^3	R^4	R^5	R^6	R^7
1	$SO_3^{\ominus}$	$SO_3^{\ominus}$	Cl	Cl	Cl	Cl	Cl
2	$SO_3^{\ominus}$	H	Cl	Cl	Cl	Cl	Cl
3	H	H	Cl	Cl	Cl	Cl	Cl
4	$SO_3^{\ominus}$	$SO_3^{\ominus}$	Cl	Cl	Cl	Cl	H
5	$SO_3^{\ominus}$	$SO_3^{\ominus}$	Cl	Cl	Cl	H	H
6	$SO_3^{\ominus}$	$SO_3^{\ominus}$	Cl	H	H	H	H



Mytilipin A (**7**)



Malhamensilipin A (**8**)



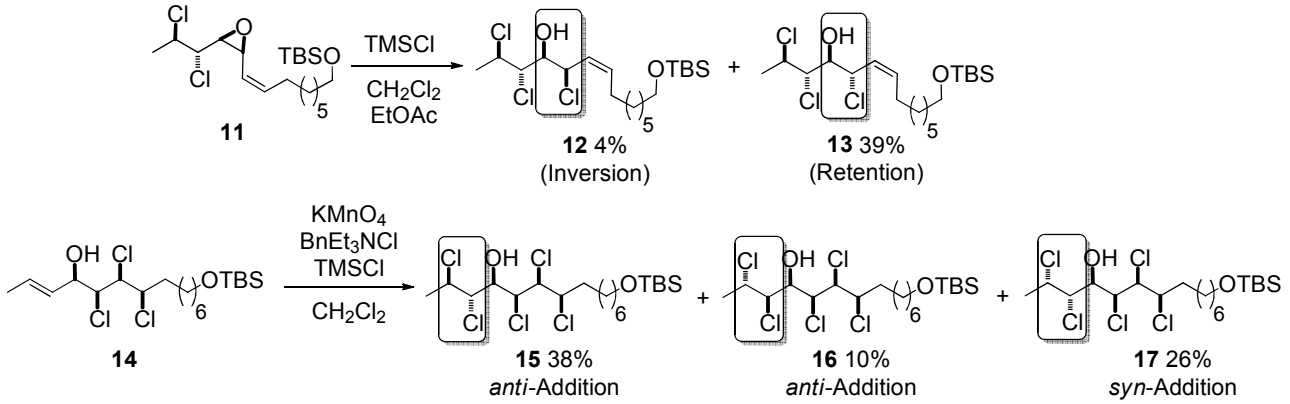
$R^1 = nC_{15}H_{31}$, R^2 = OH: Mytilipin B (**9**)
$R^1 = nC_{15}H_{31}$, R^2 = H: Mytilipin C (**10**)

Figure 1. Chlorosulfolipids (CSLs).

In order to elucidate the mechanism of the biological activity of CSLs at the molecular level, the determination of stereochemistries of CSLs is essential. However, only planar structures of CSLs were known until the 2000s due to the lack of means to elucidate their complex stereochemistries, although the absolute configuration of the simplest CSL **6** was determined in 1969.[1c] More recently, in 1994, Gerwich and Slate reported the isolation and gross structure of malhamensilipin A (**8**), a protein tyrosine kinase (PTK) inhibitor found in cultured *P. malhamensis*.[5] Finally, in 2001, Ciminiello and Fattorusso isolated mytilipins A-C (**7**,[6] **9**,[7a] and **10**[7b]) and determined their relative and absolute configurations during their search on food poisoning from mussels in the Adrian Sea. In their structure elucidation, *J*-based configuration analysis (JBCA) developed by Murata[8] was successfully utilized to arrive at the relative stereochemistries. This structure determination study was the first application of JBCA to CSLs. With this publication as a turning point, use of JBCA became widespread for the elucidation of the relative stereochemistries of CSLs. In 2009, the absolute configuration of danicalipin A (**1**) was determined. Vanderwal and Gerwick achieved the total synthesis of **1** in racemic form and assigned the relative stereochemistries of synthetic **3** using JBCA. Additionally, a sample of natural **3** obtained by Hanes more than 30 years ago was subjected to the modified Mosher's method[9] to determine the absolute stereochemistries of **1** and **3**.[10] Concurrently, Okino isolated CSLs **1**-**6** from cultured *O. danica* and elucidated their absolute configurations by a combination of JBCA and the modified Mosher's method.[11] These two reports reached the same conclusions. Moreover, Okino evaluated toxicities of **1**-**6** with brine shrimp (*Artemia salina*), with **1**, **2**, **4**-**6** showing similar toxicities and **3** showing less toxicity. This result seems to indicate that the number of chlorine atoms in CSLs does not affect their toxicity toward brine shrimp.

Because of their intriguing and unprecedented structures, CSLs have attracted a great deal of attention from synthetic organic chemists. After the first total synthesis of racemic **7**[12a] by Carreira in 2009, a milestone for the chemical synthesis of CSLs, the following total syntheses of CSLs were reported from four groups: **9**[13] by Carreira, **1**,[10] **7**,[14] and **8**[15] by Vanderwal, **1**[16] and **7**[17] by Yoshimitsu, and **1**[18] by us. From a synthetic point of view, it is necessary for the efficient construction of the polychlorinated frameworks of CSLs to stereoselectively install chloride(s) into a chlorinated scaffold. However, unexpected stereoselectivities were often found in this type of

transformation. For example, Carreira planned the synthesis of *syn*-chlorohydrin **12** from *cis*-epoxide **11** (Scheme 1).[12a] Although it is usually known that this type of S_N2 reaction by chloride anion occurs at the allylic position with stereochemical inversion, epoxide ring opening of **11** with TMSCl afforded the unexpected *anti*-chlorohydrin **13** with retention as a major product along with a trace amount of the expected *syn*-chlorohydrin **12** with inversion. Yoshimitsu attempted the synthesis of *anti*-1,2-dichloride **15** through stereospecific *anti*-1,2-dichlorination reaction of *E*-olefin **14**.[17] However, 26% of unanticipated *syn*-1,2-dichloride **17** was formed along with anticipated *anti*-1,2-dichlorides **15** (38%) and **16** (10%). The anchimeric participation of chlorides in these polychlorinated systems most likely causes the unusual stereoselectivities. This review summarizes recent total syntheses of CSLs. Special emphasis is placed on synthetic methodologies[19] for stereoselective introduction of chlorides into organic frameworks of CSLs.[20]

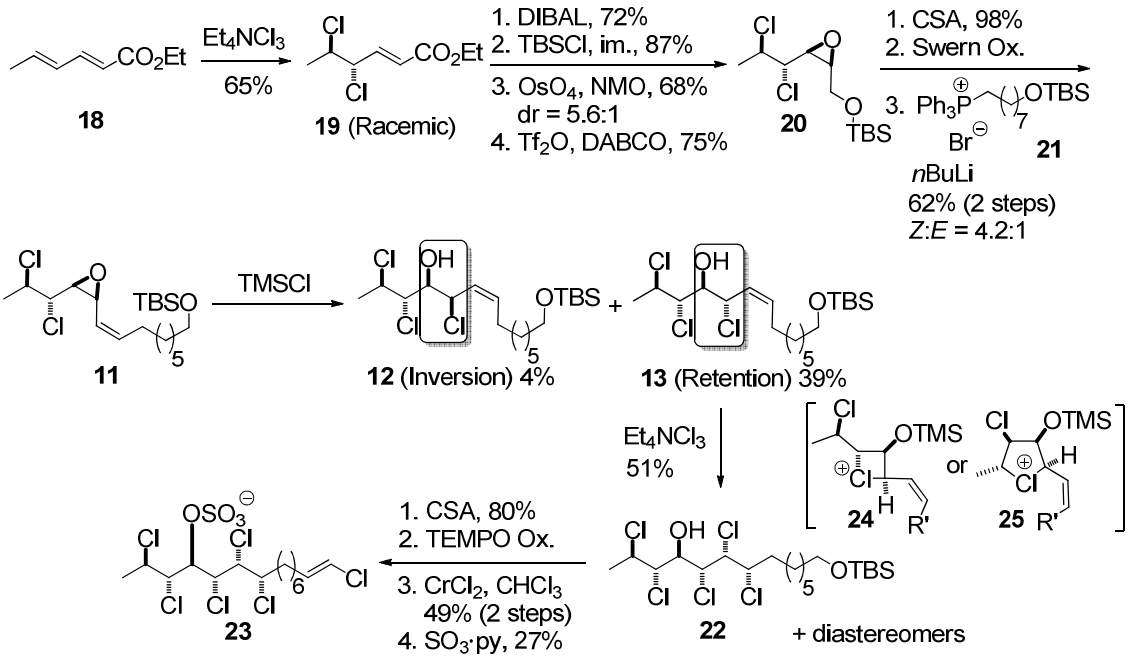


Scheme 1. Unusual stereoselectivities in total syntheses.

Carreira's synthesis

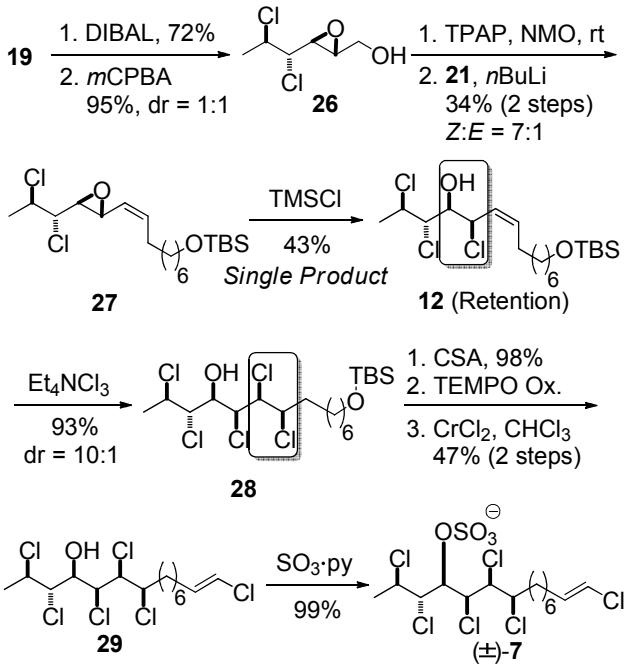
The first in a series of syntheses of CSLs, Carreira reported the first total synthesis of racemic mytilipin A (**7**) in 2009.[12a] The synthetic details are shown in Schemes 2 and 3. When commercially available ethyl sorbate (**18**) was reacted with Et_4NCl_3, stereospecific *anti*-1,2-dichlorination exclusively took place at the δ,γ-double bond, which is more electron rich than the α,β-double bond, giving racemic *anti*-1,2-dichloride **19** in 65% yield. Reduction of the ester, TBS protection, diastereoselective dihydroxylation with OsO_4 (dr = 5.6:1, see: Scheme 7), and epoxide ring closure via triflation afforded *cis*-epoxide **20**. Epoxide **20** was further transformed into *cis*-epoxide **11** as a separable *EZ* mixture (*Z*:*E* = 4.2:1) by TBS deprotection, Swern oxidation, and Wittig reaction with **21** derived from commercially available 8-bromo-1-octanol. As mentioned above, the treatment of **11** with TMSCl provided undesired *anti*-chlorohydrin **13** (39%) as a major product along with desired *syn*-chlorohydrin **12** (4%). The major diastereomer **13** was initially assumed to have the relative stereochemistry found in the natural product. Thus, **13** was transformed into chlorosulfolipid **23**. 1,2-Dichlorination of **13** gave *syn*-1,2-dichloride **22** in 51% yield along with other diastereomers. The diastereoselectivity of the 1,2-dichlorination reaction of **13** was not clear, since the reaction was performed by employing an *EZ* mixture of **13** and its *E*-isomer (*Z*:*E* = 2.6:1). However, the stereoselectivity of the 1,2-dichlorination of **13** was considered to be high, because the *anti*-1,2-dichlorination of related **12** proceeded with high diastereoselectivity (10:1) as described later (Scheme 3). Conversion of **22** into **23** was accomplished through Takai-Utimoto chloroolefination and sulfation. However, the ^{1}H-NMR spectrum of **23** was different from that of natural **7**. After careful re-examination of the NMR spectra of **12** and **13**, it was found that **13** was the epimer of **12** at the allylic position. These unexpected results have been debated as follows based

on the report by Peterson.[21] Anchimeric participation of one of the chlorides of **11** formed chloronium intermediate **24** or **25** with inversion of configuration at the allylic chiral center. This was followed by intermolecular chloride anion attack on the same allylic position of **24** or **25** with inversion. As a result, the epoxide opening of **11** occurred with net retention of stereochemistry at the allylic asymmetric center to produce **13**.



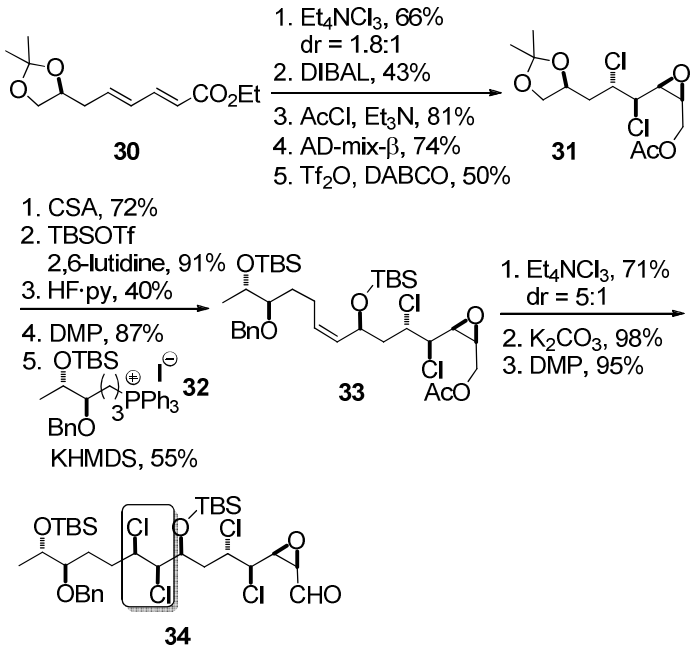
Scheme 2. Unexpected epoxide opening.

Next, the retentive epoxide opening reaction was utilized for the total synthesis of **7** (Scheme 3). The required *trans*-epoxide **27** was prepared from **19** by the following sequence: reduction of the ester, epoxidation with *m*CPBA (dr = 1:1), Ley oxidation of *trans*-epoxide **26**, and Wittig reaction with **21** (*Z*:*E* = 7:1). As anticipated, the treatment of **27** (pure *Z*-isomer) with TMSCl provided the desired *syn*-chlorohydrin **12** in 43% yield as a single product with stereoretention. By treatment of **12** with Et_4NCl_3, stereospecific *anti*-1,2-dichlorination of the *Z*-olefin occurred in a highly diastereoselective manner (dr = 10:1, see: Tables 1 and 2) to afford *syn*-1,2-dichloride **28** in 93% yield, in stark contrast to the non-stereospecific 1,2-dichlorination of *E*-olefin **14** (Schemes 1 and 11). Dichloride **28** was then converted to (±)-**7** via vinyl chloride **29** according to the same synthetic scheme as that for **23**.



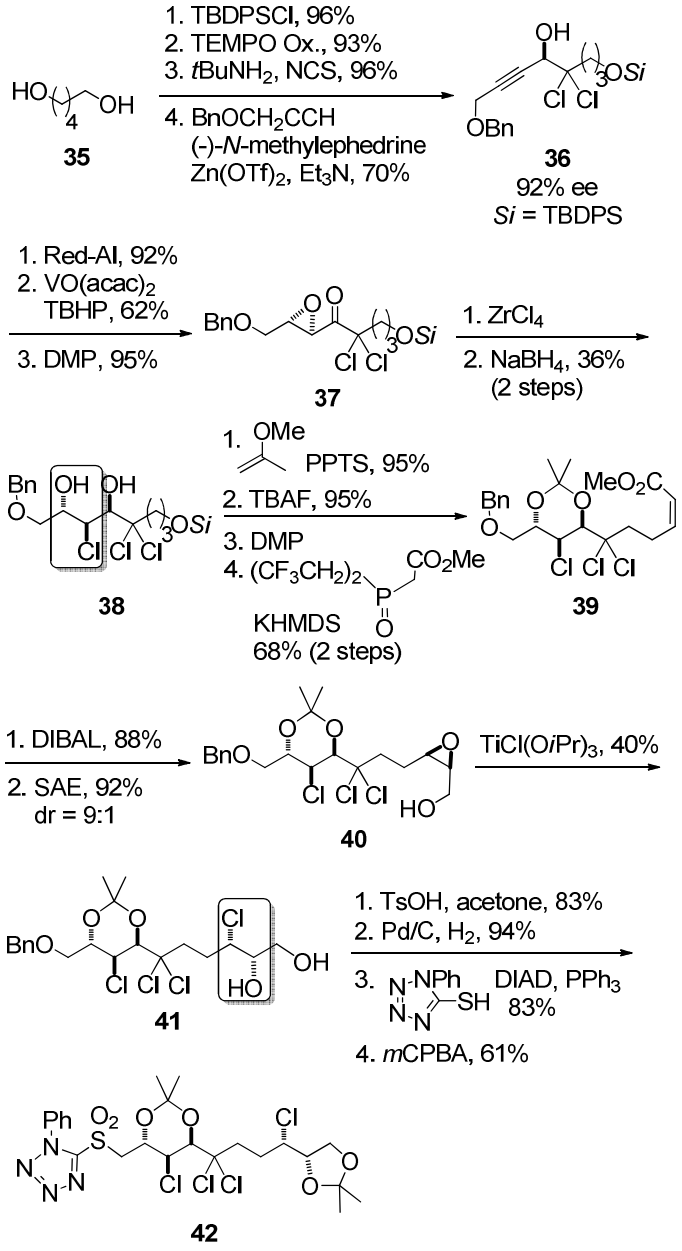
Scheme 3. Total synthesis of **7** by Carreira's group.

In 2011, this group achieved the total synthesis of (+)-mytilipin B (**9**), the most complex of the CSLs isolated to date, utilizing a Julia coupling reaction between aldehyde **34** and sulfone **42** (Schemes 4 and 5).[13] Synthesis of **34** commenced with α,β,γ,δ-unsaturated ester **30** prepared from commercially available (*S*)-1,2,4-butanetriol. While *anti*-1,2-dichlorination with Et_4NCl_3 proceeded cleanly at the γ,δ-double bond of **30**, the diastereofacial selectivity was low (dr = 1.8:1, 66%). Reduction of the ester, acetylation, Sharpless asymmetric dihydroxylation, and dehydration via triflation gave *cis*-epoxide **31** as a single stereoisomer. Next, **31** was transformed to *Z*-olefin **33** (probably only the *Z*-isomer) by a sequence involving acetonide removal, TBS protection, selective deprotection, Dess-Martin oxidation, and Wittig reaction employing phosphonium salt **32** synthesized from commercially available (*S*)-ethyl lactate. Stereospecific *anti*-1,2-dichlorination of **33** with Et_4NCl_3 (dr = 5:1, 71%, see: Tables 1 and 2) followed by deacetylation and Dess-Martin oxidation provided **34**.



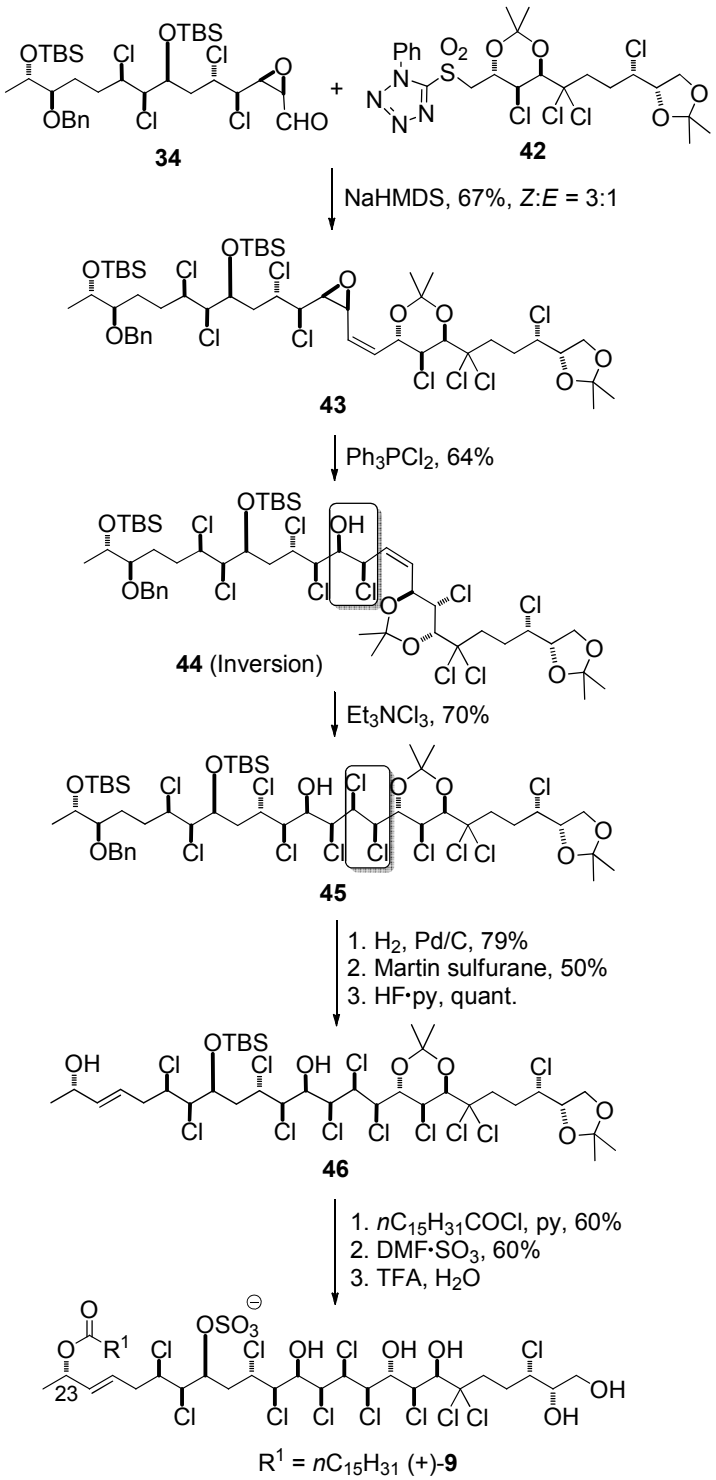
Scheme 4. Synthesis of fragment **34**.

Preparation of **42** started with commercially available 1,5-pentanediol (**35**) which was transformed to propargyl alcohol **36** in 92% ee through successive mono-TBDPS protection, TEMPO oxidation, α,α-dichlorination with NCS and *t*BuNH$_2$, and enantioselective Zn-acetylide addition to α,α-dichloroaldehyde (Scheme 5).[23] Conversion of **36** into α-epoxyketone **37** commenced with alkyne semireduction, VO(acac)$_2$-catalyzed epoxidation, and Dess-Martin oxidation. Regioselective epoxide ring opening of **37** with $ZrCl_4$ followed by reduction of α-chloroketone afforded *anti*-chlorohydrin **38** in 36% yield (2 steps). *Z*-α,β-Unsaturated ester **39** was synthesized from **38** by successive acetonide protection, removal of the TBDPS group, Dess-Martin oxidation, and Still *Z*-olefination. After reduction of the ester, Sharpless asymmetric epoxidation (dr = 9:1) gave *cis*-epoxide **40**. Treatment of **40** with TiCl(O*i*Pr)$_3$ resulted in epoxide opening with inversion to yield *syn*-chlorohydrin **41** in 40% yield, but the regioselectivity was low (1,2-diol:1,3-diol = 2:3). The synthesis of **42** was completed following acetonide formation, benzyl ether cleavage, Mitsunobu displacement with phenyltetrazolylsulfide, and oxidation to the sulfone.



Scheme 5. Synthesis of fragment **42**.

The crucial Julia coupling reaction between **34** and **42** gave allylic *cis*-epoxide **43** (*Z*:*E* = 3:1) (Scheme 6). Remarkably, epoxide opening of **43** with PPh_3Cl_2[24] proceeded with inversion to give desired *syn*-chlorohydrin **44** in 64% yield (from *ZE*-mixture). The ring opening of allylic epoxide **43** did not suffer interference from neighboring chlorides. In stark contrast, anchimeric participation of neighboring chlorides took place over the stereochemical course of retentive epoxide openings of related allylic epoxides **11** and **27** (Schemes 2 and 3). *anti*-1,2-Dichlorination of **44** with Et_4NCl_3 produced *syn*-1,2-dichloride **45** in 70% yield with high diastereoselectivity (see: Tables 1 and 2). After deprotection of the benzyl ether, *E*-olefin formation with Martin sulfurane followed by removal of the TBS groups gave *E*-olefin **46**. Finally, regioselective palmitoylation of the triol, regioselective sulfation of the diol, and removal of the acetonide groups were performed to deliver the proposed structure of mytilipin B. However, the ^{1}H-NMR spectrum of synthetic **9** differed from that of the natural sample. Careful reconsideration of the data available in the isolation report of mytilipin B led to concerns about the assignment of the stereochemistry at C23. Carreira thus suggested that mytilipin B is the C23-epimer of the structure reported in the isolation paper. This configurational uncertainty will likely be resolved only through chemical synthesis.



Scheme 6. Total synthesis of **9**.

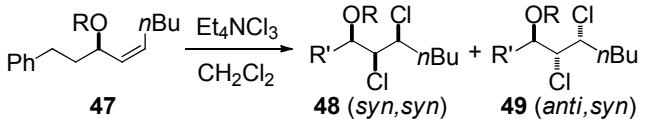
Vanderwal's synthesis

Vanderwal investigated the diastereoselectivity of stereospecific *anti*-1,2-dichlorination of a series of *Z*-allylic alcohol derivatives, on the assumption that allylic strain ($A_{1,3}$) serves as a valuable stereocontrol element.[25] Preliminary experiments were carried out using several different allylic alcohol derivatives with two molecular chlorine surrogates, Et_4NCl_3 (Mioskowski reagent)[26] and $BnEt_3NCl$-$KMnO_4$-TMSCl (Markó reagent),[27] to reveal nearly identical levels of efficiency and diastereoselectivity with both reagents. Therefore, Et_4NCl_3, an easily prepared, bench-stable solid, was employed for further studies. The results in Table 1 indicate that 1,2-dichlorination of **47** took place cleanly in a diastereoselective manner with *anti* stereospecificity to afford

syn,*syn*-dichloride **48** as a major stereoisomer along with *anti*,*syn*-dichloride **49**. Although the steric bulkiness of the substituent groups on the allylic alcohol oxygen had little effect on selectivity, electron-deficient acyl groups led to reasonable margins of selectivity. Particularly, pivaloyl, trichloroacetyl, and trifluoroacetyl groups showed significant diastereoselectivities with the best results at –90 °C. However, dichlorinations of pivaloate esters generated substantial side products resulting from ester migration, and trifluoroacetate esters were labile to chromatographic purification. Thus, the trichloroacetate group was deemed optimal, despite the slightly diminished selectivities. As shown in Table 2, the *anti*-1,2-dichlorination reactions of allylic trichloroacetates **50** yielded *syn*,*syn*-dichloride **51** with usable stereoselectivities (4.6:1 to >20:1) and reasonable functional group tolerance across a range of structurally different substrates. The *syn*,*syn*-hydroxydichloride stereotriad found in **51** is prevalent in CSLs. In fact, the *syn*,*syn*-hydroxydichloride stereotriad motif was successfully constructed through diastereofacially selective *anti*-1,2-dichlorination of *Z*-olefin **33** in Carreira's total synthesis of **9**. Furthermore, during Carreira's total syntheses of **7** and **9**, *syn*,*syn*-1,2,3-trichlorides **28**, **22**, and **45** were derived from *Z*-olefins **12**, **13**, and **44**, respectively, with high diastereofacial selectivity via stereospecific *anti*-1,2-dichlorination. Clearly, allylic chloride groups directed facial selectivity of these 1,2-dichlorination reactions. Since the dichlorinations of polychlorinated *Z*-olefins always proceeded with *anti* stereospecificity to produce *syn*-1,2-dichlorides exclusively, anchimeric assistance of the distal chlorine atom did not occur during 1,2-dichlorinations of *Z*-olefins. Therefore, this synthetic procedure is one of the most powerful methods capable of incorporating an array of chlorine atoms into hydrocarbon skeletons of CSLs with correct absolute stereochemistries.

Table 1.

Optimization of protective group with *Z*-allyl alcohol derivatives.



47 **48** (*syn,syn*) **49** (*anti,syn*)

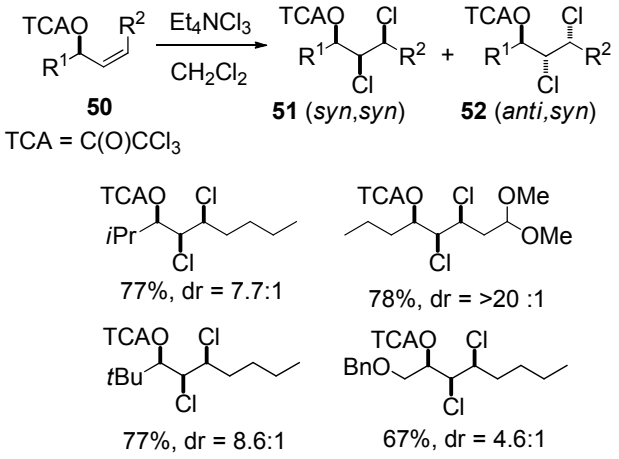
R' = $(CH_2)_2Ph$

R	temp. (°C)	**48**:**49**	R	temp. (°C)	**48**:**49**
H	-78	1.0:1	Piv	-78	7.5:1[a]
Me	-78	2.0:1	Piv	-90	7.7:1[a]
TBS	-78	2.0:1	Cl_3CCO	-78	5.0:1
CO_2Me	-78	5.0:1[a]	Cl_3CCO	-90	6.5:1
Boc	-78	5.0:1[a]	F_3CCO	-78	6.0:1
Ac	-78	5.0:1[a]	F_3CCO	-90	7.0:1

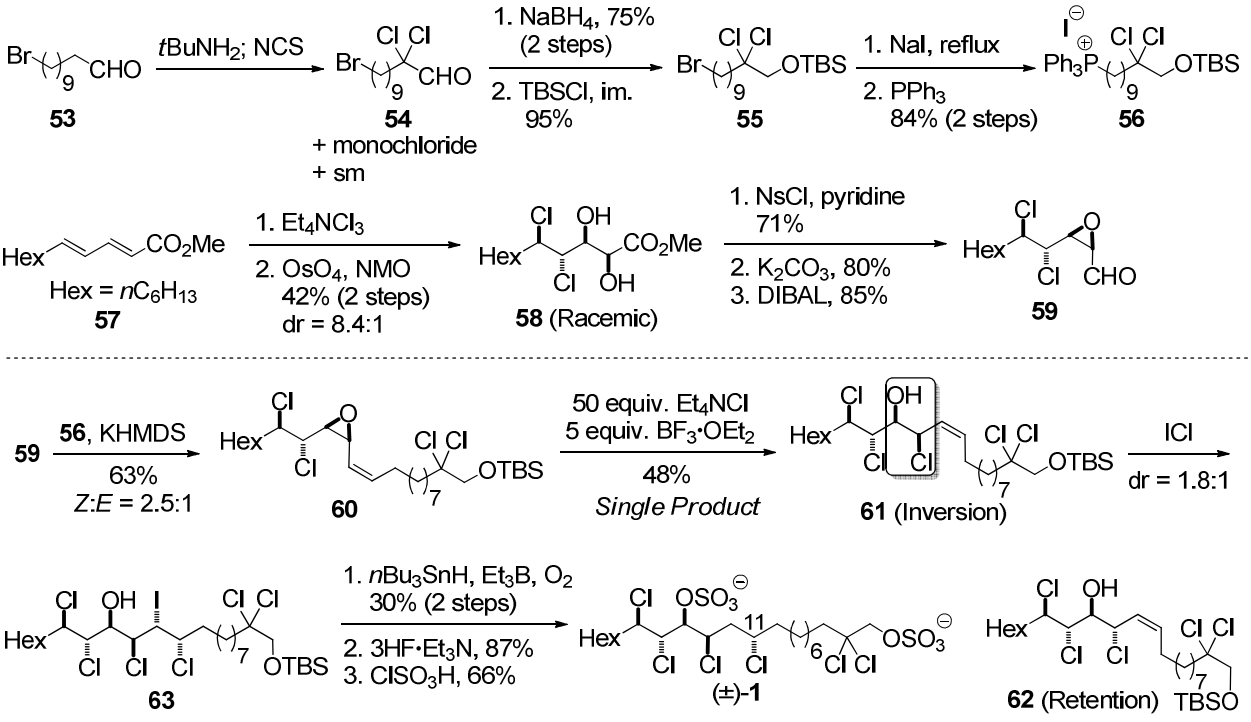
[a] Rearranged products were formed.

Table 2.

Selectivity of 1,2-dichlorination.



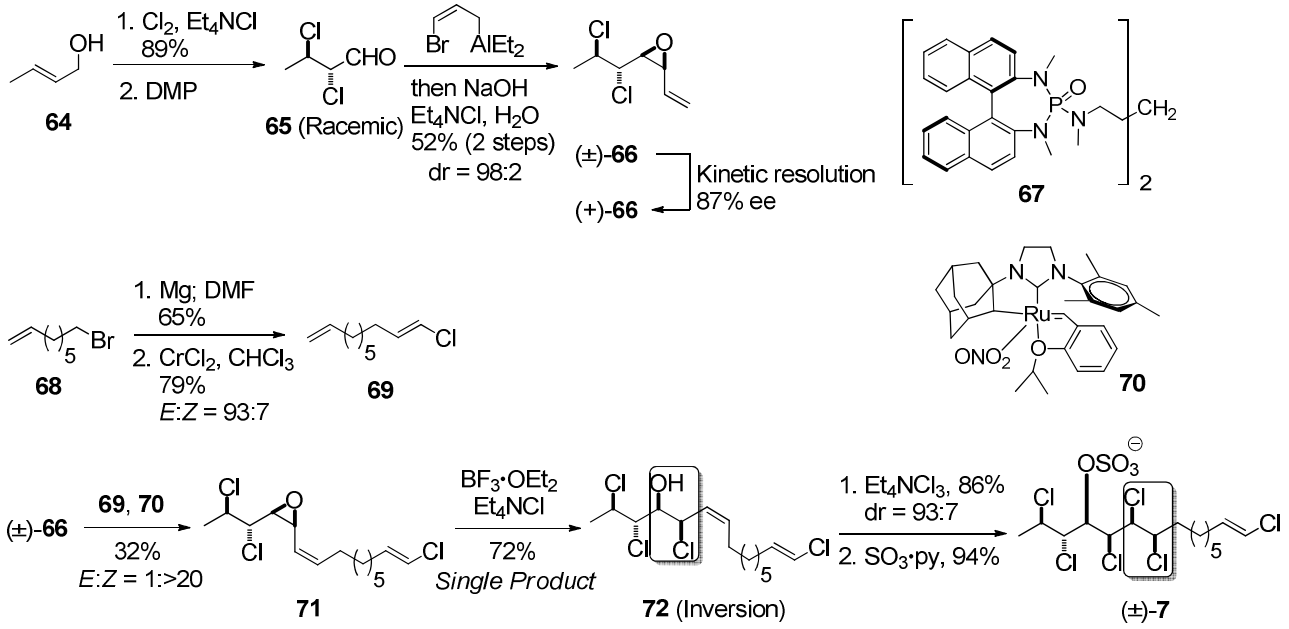
Vanderwal achieved the total synthesis of (±)-danicalipin A (**1**) via Wittig reaction of aldehyde **59** using phosphonium salt **56** (Scheme 7).[10] The synthesis of **56** started from known 11-bromoundecanal (**53**) which upon treatment with NCS and *t*BuNH$_2$[22] gave α,α-dichloride **54** (71% yield as TBS ether **55**) contaminated with small amounts of α-monochloride and starting material. Eventually, pure **56** was obtained by reduction of the aldehyde, TBS protection, iodination of **55**, and treatment with PPh_3. α,β,γ,δ-Unsaturated ester **57**, prepared through Mizoroki-Heck reaction of known (*E*)-1-iodo-1-octene with methyl acrylate, was subjected to stereospecific *anti*-1,2-dichlorination with Et_4NCl_3 and dihydroxylation with OsO_4 (dr = 8.4:1) to give diol **58** in racemic form in 42% yield (2 steps). The diastereofacial selectivity of the OsO_4 oxidation was rationalized with the model proposed by Kishi,[28] as well as the result observed in the OsO_4 oxidation of **19** (Scheme 2). Epoxide ring closing through regioselective nosylation, and reduction of the ester to an aldehyde afforded **59**.



Scheme 7. Total synthesis of **1** by Vanderwal's group.

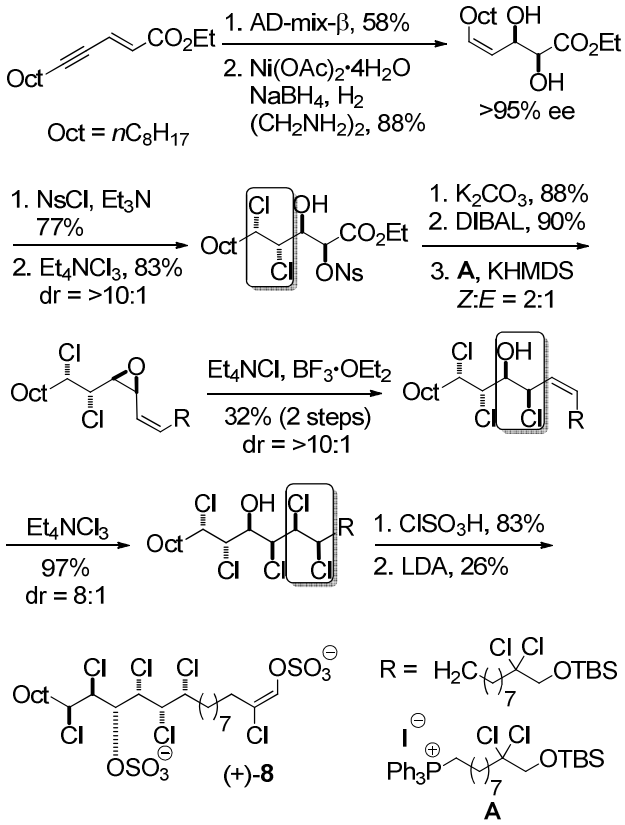
Wittig reaction of **56** and **59** produced allylic *cis*-epoxide **60** (*Z*:*E* = 2.5:1). As reported by Carreira, treatment of **60** with TMSCl resulted in the formation of undesired *syn*-chlorohydrin **62** with retention in 38% yield (from *Z*-isomer) as the major diastereomer along with desired *syn*-chlorohydrin **61** with inversion (dr = 6:1). Empirical studies led to the use of excess BF_3-OEt_2 and Et_4NCl to give **61** in 48% yield from the *ZE* mixture of **60** (67% based on *Z*-isomer). Stereospecific *anti*-1,2-iodochlorination of **61** afforded **63** with complete regioselectivity but poor diastereofacial selectivity (1.8:1) in contrast to the *anti*-1,2-dichlorinations as described so far. After radical deiodination with nBu_3SnH followed by chromatographic separation of the C11-epimers, total synthesis of (±)-**1** was achieved by removal of the TBS group and sulfation.

Recently, Vanderwal reported the highly effective total synthesis of mytilipin A (**7**) in which the longest linear sequence of steps was only seven for racemic **7**, and eight for optically active **7** (Scheme 8).[14] Crotyl alcohol (**64**) was converted into racemic *anti*-1,2-dichloride in 87% yield using molecular chlorine and Et_4NCl (presumably *in situ* generation of Et_4NCl_3). After Dess-Martin oxidation, $CBrH{=}CHCH_2AlEt_2$[29] added to aldehyde **65** with high diastereoselectivity (dr = 98:2), consistent with both the Felkin-Anh and Cornforth models,[30] and the bromohydrin was transformed to *cis*-epoxide (±)-**66** by treatment with aqueous base. The olefin partner **69** required for the convergent step was synthesized from commercially available 8-bromo-1-octene (**68**) by formylation of the Grignard reagent generated from **68** and Takai-Utimoto chloroolefination. *Z*-Selective olefin cross-metathesis of (±)-**66** and **69** employing Grubbs catalyst **70**[31] afforded allylic *cis*-epoxide **71** with complete control of olefin geometry. Construction of the *syn*,*syn*-1,2,3-trichloride stereotriad motif of **7** was carried out according to the synthetic scheme described above. Epoxide opening of **71** produced *syn*-chlorohydrin **72** in 72% yield in the presence of excess BF_3-OEt_2 and Et_4NCl with complete stereoinversion. Stereospecific *anti*-1,2-dichlorination of **72** with Et_4NCl_3 occurred with excellent diastereofacial selectivity (dr = 93:7) in 86% yield and subsequent sulfation furnished (±)-**7**. For the chiral synthesis of **7**, (±)-**66** was resolved through chlorinolysis mediated by (*R*,*R*)-Denmark catalyst **67**[32] to yield (+)-**66** in 87% ee. The synthesis of (–)-**7**, the enantiomer of natural (+)-**7**, was accomplished by the use of resolved (+)-**66**.



Scheme 8. Total synthesis of **7** by Vanderwal's group.

In 2010, the same researchers achieved the total synthesis of (+)-malhamensilipin A (**8**).[15] In the total synthesis, formation of the *syn*,*syn*-1,2,3-trichloride stereotriad motif of **8** was successfully performed with high stereoselectivities through successive allylic epoxide opening with inversion by BF_3-OEt_2 and Et_4NCl and stereospecific *anti*-1,2-dichlorination with Et_4NCl_3. The synthetic scheme is shown in Scheme 9. Some details of the total synthesis have been omitted for lack of space.



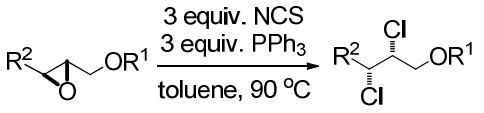
Scheme 9. Total synthesis of **8** by Vanderwal's group

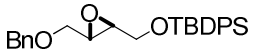
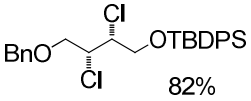
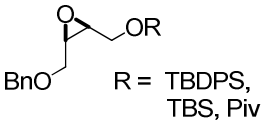
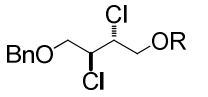
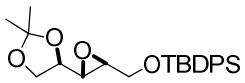
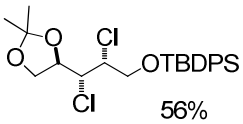
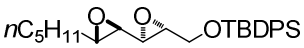
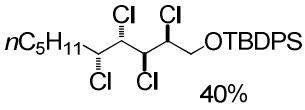
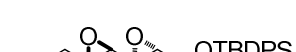
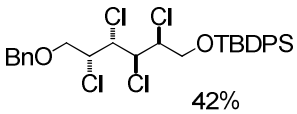
Yoshimitsu's synthesis

Yoshimitsu described an effective synthetic method for enantioselective construction of the polychlorinated hydrocarbon motifs of CSLs by means of multiple nucleophilic chlorinations of chiral epoxides with NCS and PPh_3 (Table 3).[33] Although a direct approach to chiral 1,2-dichlorides from epoxides in a stereospecific manner has been reported, little is known about the general scope of the 1,2-deoxydichlorination reactions of structurally complex internal epoxides.[34] After extensive optimizations, they found that stereospecific 1,2-deoxydichlorination of an epoxide cleanly proceeds by treatment with 3 equiv. of NCS and 3 equiv. of PPh_3 in toluene at 90 °C. Representative examples are shown in Table 3. 1,2-Deoxydichlorination of *cis*- and *trans*-epoxides provided *anti*-1,2- and *syn*-1,2-dichlorides, respectively, in good yields (56% to 84%) with good functional group compatibility. The stereochemistry of the products was consistently inversion at both stereogenic centers. Moreover, 1,2,3,4-tetrachlorides were also produced in one step from chiral bisepoxides by the use of NCS and Ph_3P. The stereospecific 1,2-deoxydichlorination of chiral epoxides would provide novel short access to the structural motifs of CSLs, particularly, *anti*-1,2-dichloride motifs.

Table 3.

1,2-Dichlorination from epoxide.

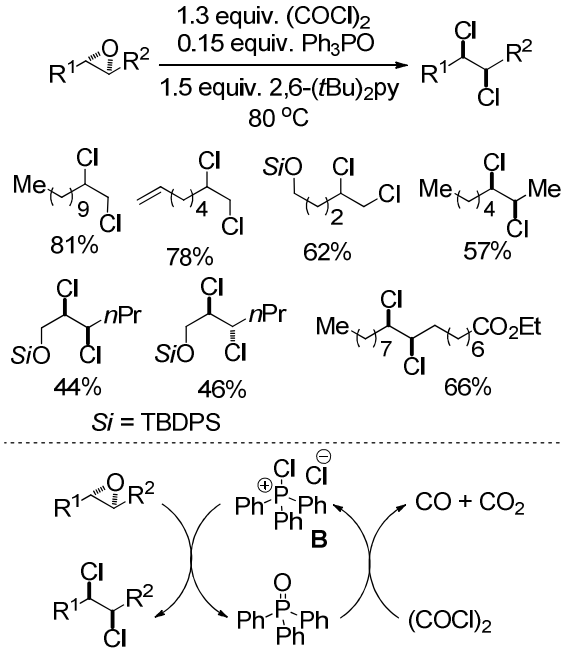


substrate	product
	 82%
 R = TBDPS, TBS, Piv	 69-84%
	 56%
	 40%
	 42%

Denton developed the stereospecific O=PPh_3-catalyzed 1,2-deoxydichlorination of epoxides with $(COCl)_2$.[35] As illustrated in Table 4, the reaction was effective for a variety of epoxides with yields ranging from moderate to excellent (44% to 81%). They proposed a catalytic cycle in which chlorophosphonium salt **B**, generated *in situ* from O=PPh_3 and $(COCl)_2$ with concomitant loss of CO and CO_2, was effective for the 1,2-deoxydichlorination of epoxides.

Table 4.

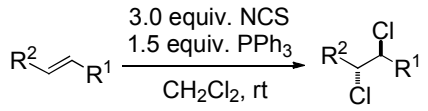
Ph_3PO-Catalyzed 1,2-dichlorination from epoxide.

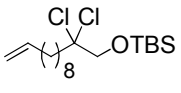
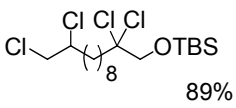
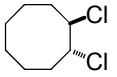
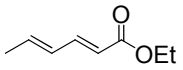
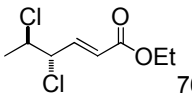
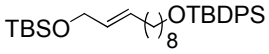
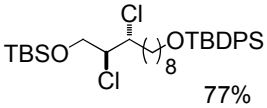
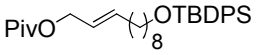
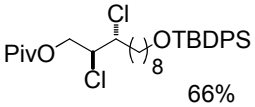
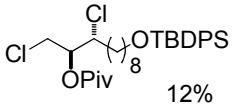


Additionally, in 2013, Yoshimitsu demonstrated that the combination of NCS and Ph_3P also promoted stereospecific *anti*-1,2-dichlorinations of olefins by serving as a molecular chlorine surrogate by modification of the reagent stoichiometry.[36] The reaction was carried out with 3.0 equiv. of NCS and 1.5 equiv. of PPh_3 in CH_2Cl_2 at room temperature. Typical examples are shown in Table 5 which indicates that the *anti*-1,2-dichlorination reaction is tolerant of some functional groups. Interestingly, dichlorination with NCS and Ph_3P of allyl pivaloate generated an ester-migrated product similar to that of dichlorination with Et_4NCl_3 described by Vanderwal (see: Table 1).

Table 5.

1,2-Dichlorination of olefin with NCS and PPh_3.

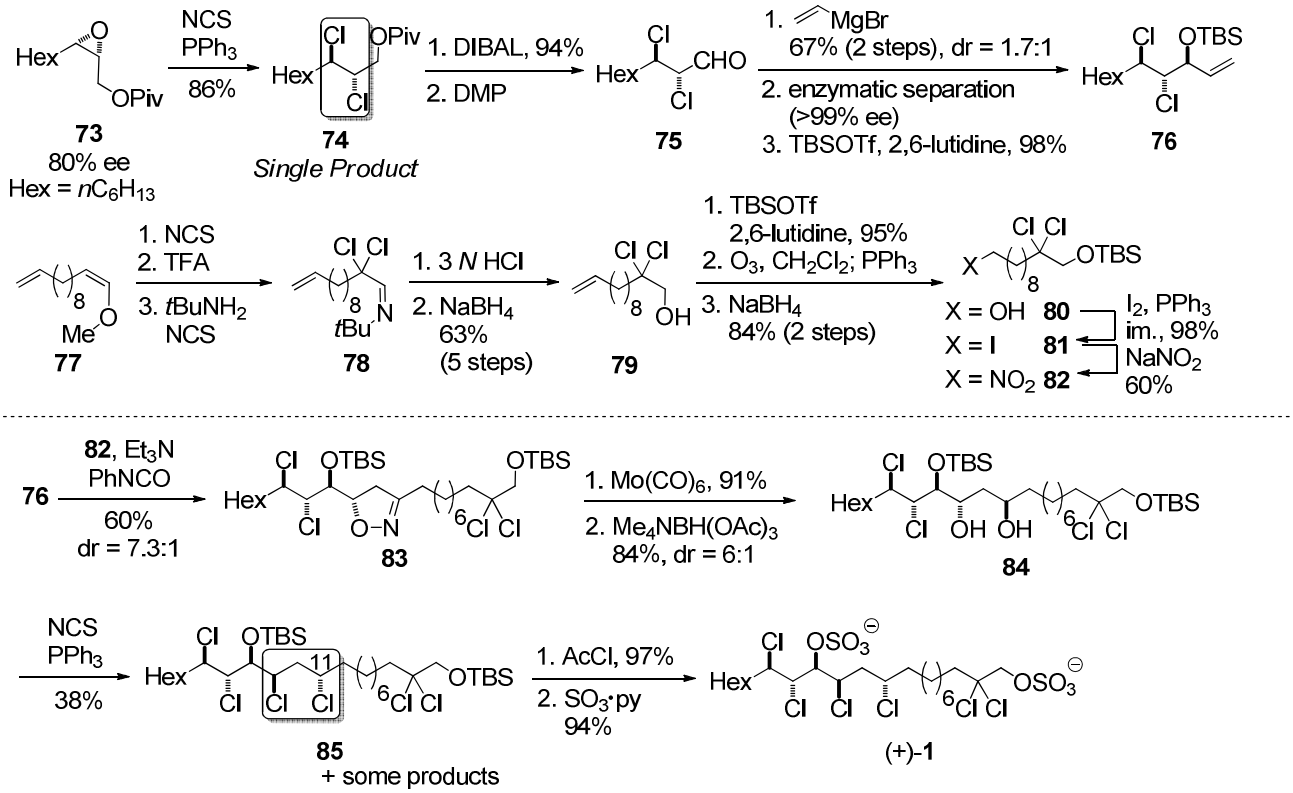


substrate	product
	 89%
	 93%
	 76%
	 77%
	 66%  12%

In 2011, Yoshimitsu reported the total synthesis of (+)-danicalipin A (**1**), which featured the coupling reaction between olefin **76** and nitro compound **82** (Scheme 10).[16] The synthesis of **76** was initiated by 1,2-deoxydichlorination with NCS and PPh_3 of *cis*-epoxide **73**, derived from commercially available (*Z*)-2-nonene-1-ol via Sharpless asymmetric epoxidation (80% ee), to give *anti*-1,2-dichloride **74** in 86% yield with complete stereospecificity. Removal of the pivaloyl group and Dess-Martin oxidation yielded aldehyde **75**. After addition of CH_2=CHMgBr to **75** (dr = 1.7:1), enzymatic separation of the major epimeric alcohol by employing Lipase PS IM Amano followed by TBS protection afforded enantiomerically pure **76**. The preparation of **82** started from diene **77** (*E*:*Z* = 3:2), which was synthesized via the Wittig methoxyolefination of commercially available 10-undecenal. Stepwise 1,2-dichlorination of methoxyolefin with NCS, acidic hydrolysis, and α-chlorination of the α-chloroaldehyde with NCS and *t*$BuNH_2$ provided α,α-dichloroimine **78**, which was further transformed to alcohol **79** by acidic hydrolysis and reduction of the aldehyde. TBS protection, ozonolysis, reduction of the aldehyde, iodination of **80**, and substitution of **81** with $NaNO_2$ yielded **82**.

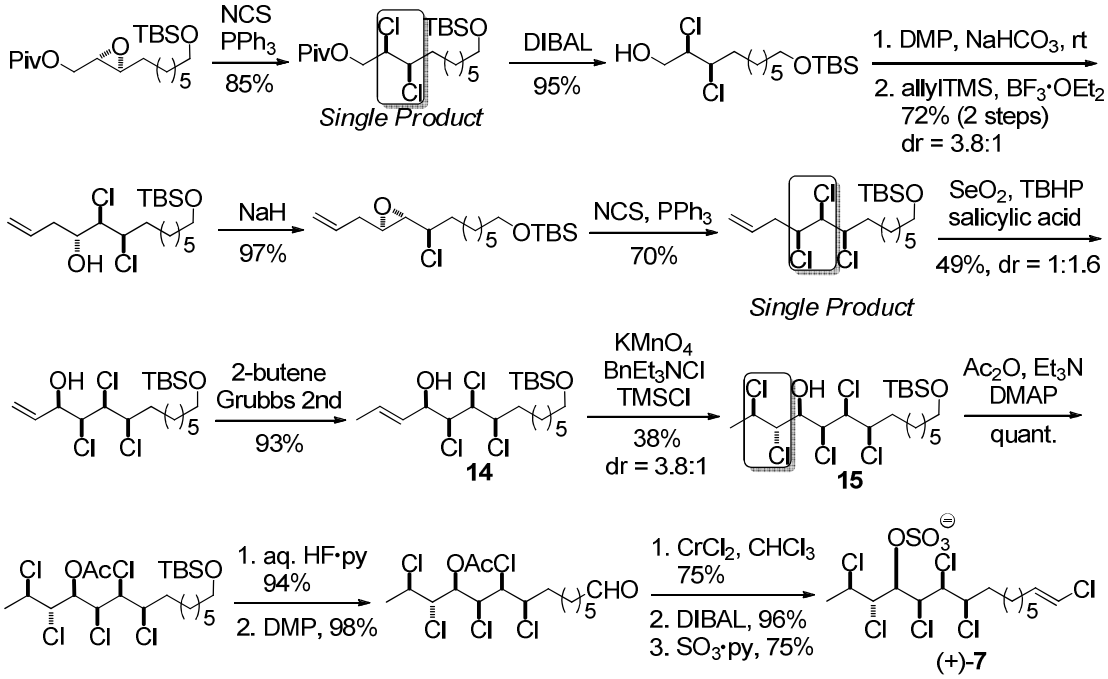
1,3-Dipolar cycloaddition with **76** and **82** under Mukaiyama conditions[37] afforded *anti*-isooxazoline **83** in a 7.3:1 epimeric mixture. The preferential formation of desired **83** can be rationalized by considering a transition state model for 1,3-dipolar cycloaddition proposed by Houk.[38] Reductive NO bond cleavage with $Mo(CO)_6$ and subsequent *anti*-1,3-reduction of the β-hydroxyketone gave *anti*-1,3-diol **84** (dr = 6:1). When **84** was reacted with NCS (3 equiv.) and PPh_3 (3 equiv.), *anti*-1,3-dichloride **85** with inversion of configuration at both asymmetric centers was obtained as a major isomer in 38% yield along with its C11-epimer (5%). The 1,3-deoxydichlorination most likely suffered from interference by the distal chlorine atoms. Finally, total synthesis of (+)-**1** was completed

through deprotection of the TBS groups and sulfation.



Scheme 10. Total synthesis of **1** by Yoshimitsu's group.

In 2010, they also achieved the total synthesis of (+)-mytilipin A (**7**).[17] During the total synthesis, the *syn,syn*-1,2,3-trichloride stereotriad of **7** was efficiently constructed with high stereoselectivities by the use of stereospecific 1,2-deoxydichlorination reactions of *trans*-epoxides. The synthetic pathway is illustrated in Scheme 11. Again, details of the total synthesis were omitted due to space considerations.

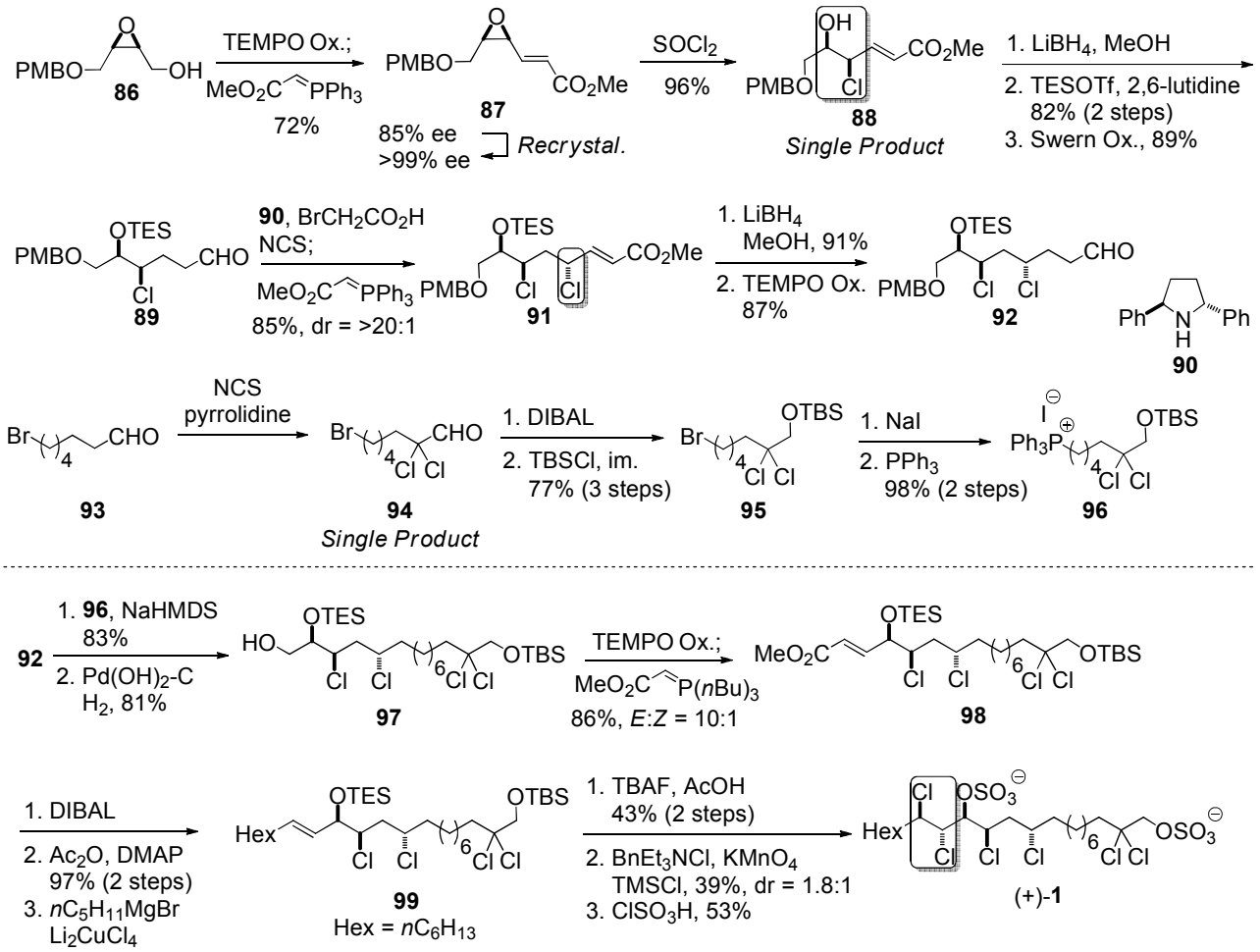


Scheme 11. Total synthesis of **7** by Yoshimitsu's group.

Umezawa/Matsuda's synthesis

In 2011, the authors reported the total synthesis of (+)-danicalipin A (**1**) (Scheme 12),[18] in which Wittig coupling reaction between aldehyde **92** and phosphonium salt **96** was employed as the convergent step. The synthesis of **92** commenced with known *cis*-epoxide **86** derived from commercially available (*Z*)-2-butene-1,4-diol via Sharpless asymmetric epoxidation (85% ee). α,β-Unsaturated ester **87** was obtained by TEMPO oxidation and Wittig reaction in a one-pot operation. After purification by recrystallization, epoxide ring opening with stereochemical inversion occurred cleanly by treatment of enantiomerically pure **87** with $SOCl_2$[39] to give *syn*-chlorohydrin **88** in 96% yield as the sole product. Reduction of the α,β-unsaturated ester, TES protection, and Swern oxidation provided aldehyde **89**. After extensive investigations, the diastereoselective α-chlorination reaction of **89** with (*R*,*R*)-2,5-diphenylpyrrolidine **90**, Jørgensen catalyst,[40] was found to achieve almost complete diastereoselectivity without any formation of the α,α-dichloroaldehyde, furnishing a labile α-chloroaldehyde which was isolated as the α,β-unsaturated ester **91** in 85% yield (2 steps) by adding a Wittig reagent in a one-pot operation. Since the α-chlorination proceeded without interference from the neighboring chloride, this α-chlorination would provide a reliable method to introduce a chlorine atom into the polychlorinated hydrocarbon skeletons of CSLs with desired absolute stereochemistry by using the proper enantiomeric catalyst **90** or *ent*-**90**. Successive reduction of the α,β-unsaturated ester and TEMPO oxidation yielded aldehyde **92**. For preparation of the other coupling partner **96**, known aldehyde **93**, prepared from commercially available 7-bromo-1-heptanol, was cleanly α,α-dichlorinated by treatment with NCS in the presence of a catalytic amount of pyrrolidine to provide pure α,α-dichloroaldehyde **94** (77% yield as TBS ether **95**) without the formation of byproducts such as α-monochloroaldehyde. Reduction of the aldehyde, TBS protection, iodination of **95**, and treatment with PPh_3 converted **94** to **96**.

Wittig reaction between **92** and **96** followed by hydrogenation of the olefin concurrent with cleavage of the PMB group gave alcohol **97**. TEMPO oxidation and subsequent Wittig reaction[41] in a one-pot operation furnished *E*-α,β-unsaturated ester **98** (*E*:*Z* = 10:1). *E*-Olefin **99** was obtained through reduction of the ester, acetylation, and allylic substitution with $nC_5H_{11}MgBr$ and Li_2CuCl_4.[42] After removal of the silyl groups, stereospecific *anti*-1,2-dichlorination of the *E*-olefin occurred cleanly by using $BnEt_3NCl$-$KMnO_4$-TMSCl (Markó reagent)[27] in octane at 90 °C to give the *anti*,*anti*-dichloride in 39% yield along with another *anti*-adduct, *syn*,*anti*-dichloride, in 28% yield (dr = 1.8:1). Disulfation at the two hydroxyl groups achieved the total synthesis of (+)-**1**.



Scheme 12. Total synthesis of **1** by Matsuda's group.

Conclusion

In this digest, the authors summarize the total syntheses of chlorosulfolipids (CSLs), a fascinating class of natural products featuring highly chlorinated hydrocarbon scaffolds, by focusing on synthetic methods for stereoselective polychlorination of the organic frameworks of CSLs. Although CSLs were first isolated in 1962, chemical synthesis of CSLs has been hampered due to the lack of synthetic methods for stereoselective polychlorination of hydrocarbon frameworks. Since Carreira's first total synthesis of a member of the CSLs in 2009, several groups, including our own, have achieved total syntheses of CSLs. During the total syntheses, unanticipated stereoselectivities were discovered in attempts to stereoselectively chlorinate hydrocarbon frameworks bearing chlorine atom(s). These chlorination reactions suffered interference from the neighboring chlorides that lowered stereoselectivities and chemical yields. By overcoming this disadvantage, important progress has been made in the development of reliable synthetic methods for stereoselective polychlorination. For example, *syn*,*syn*-1,2,3-trichloride stereotriads, a common motif in CSLs, were effectively constructed by a combination of ring opening of a *Z*-allylic epoxide with chloride and *anti*-1,2-dichlorination of the resulting *Z*-olefin. These total syntheses should facilitate biological studies on CSLs because of the difficulty of acquiring sufficient quantities of CSLs from natural sources.[43]

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43. After total synthesis of (+)-danicalipin A (**1**) as mentioned above, we investigated the toxicities toward brine shrimp (*Artemia salina*) of (+)-**1** and (–)-*ent*-**1**, synthesized via the scheme same to that for (+)-**1** from *ent*-**86**. Remarkably, (–)-*ent*-**1** showed almost the same toxicity as (+)-**1** to indicate that the absolute configuration of **1** has no effect on its toxicity in brine shrimp, see: Ref. 18.