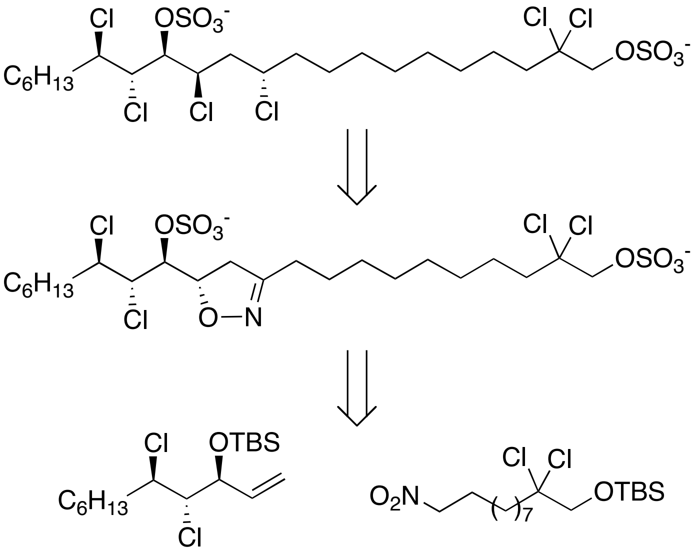


Asymmetric Total Synthesis of (+)-Danicalipin A

Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T. Org. Lett. ASAP

Current literature
Yongzhao Yan
February 26th 2011

Chlorosulfolipids

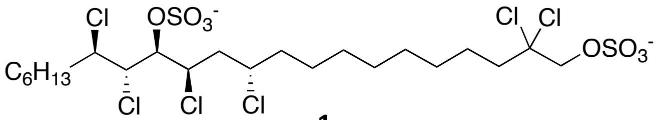
Chlorosulfolipids was first reported in 1969 and ignored by synthetic chemists for the ensuing 40 years.

Danicalipin A (**1**) was isolated by Haines and Block from *Ochromaonas danica*. It is a key component of **algal membranes**.[1]

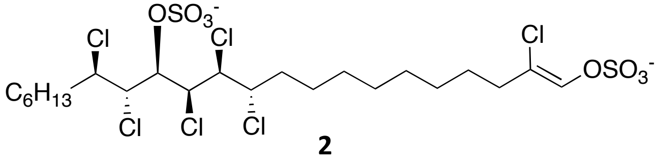
Malhamensilipin A (**2**) is isolated in 1994 from alga *O. malhamensis*. It displays activity in **kinase assay**.[2]

Ciminiello and Fattorusso reported isolation of 3-5 from Adriatic mussels. These lipids were deemed to be the causative agents in **seafood poisoning**.[3]

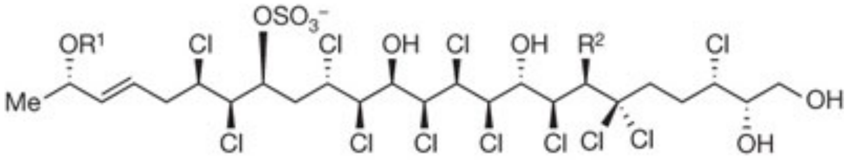
-Heavily chlorinated linear hydrocarbon motifs
-Complicated stereochemical structures
-Toxicity mechanism



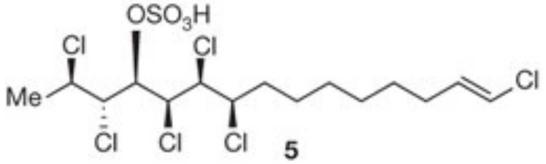
1



2



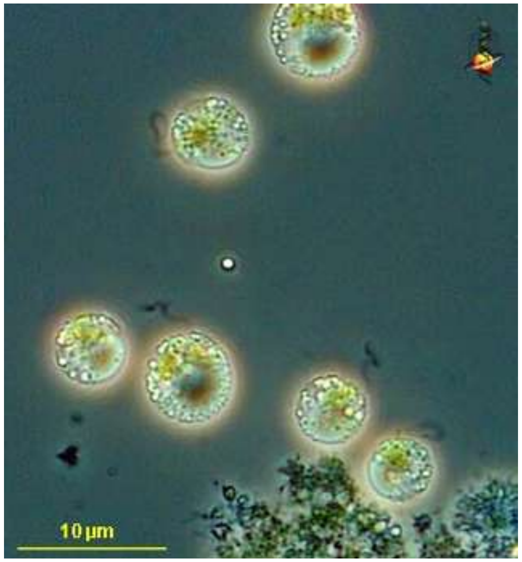
$R^1 = C(O)C_{15}H_{31}$, $R^2 = OH$ (**3**) $R^1 = C(O)C_{15}H_{31}$, $R^2 = H$ (**4**)



5

1. T. H. Haines, M. Pousada, B. Stern and G. L. Mayers, *Biochem. J.*,1969, 113, 565–566.
2. J. L. Chen, P. J. Proteau, M. A. Roberts, W. H. Gerwick, D. L. Slateand R. H. Lee, *J. Nat. Prod.*, 1994, 57, 524–527.
3. P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno,M. Di Rosa, A. Ianaro and R. Poletti, *J. Am. Chem. Soc.*, 2002, 124,13114–13120.

Danicalipin A

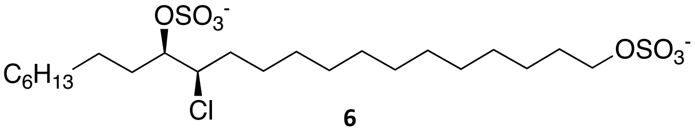


In *Ochromaonas danica* cells, the total sulfolipid fraction constitutes about 15% of the lipids and 3% of dry weight.

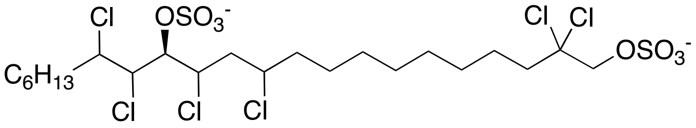
The structure of the monochloride diol 6 was determined by mass-spectroscopy.

The planar structure of the major chlorosulfolipid is elucidated by a strategy using ^{36}Cl-labeled chlorosulfolipid.[1]

These compounds were revisited in 2009 by Vanderwal by synthesis and *J*-based configurational analysis.[2]

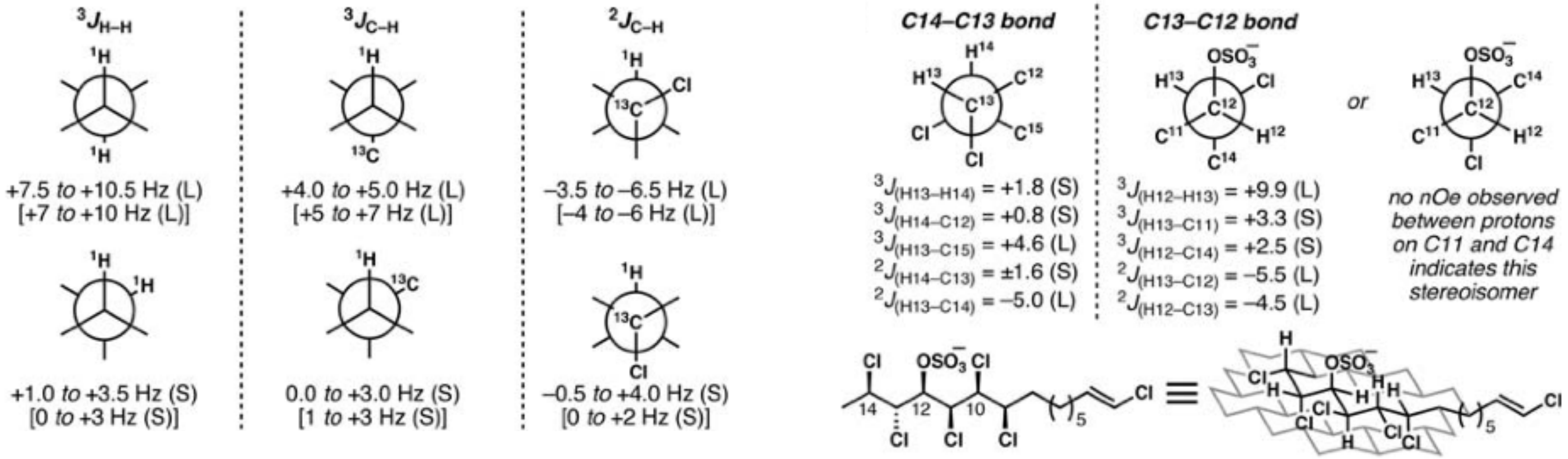


6



1. J. Elovson and P. R. Vagelos, *Proc. Natl. Acad. Soc. USA*, 1969, 62,957–963.
2. T. Kawahara, Y. Kumaki, T. Kamada, T. Ishii and T. Okino*, J. Org.Chem.,* 2009, 74, 6016–6024.

Elucidation of relative configuration of chlorosulfolipid



Carreira et al., applied Murata's approach for the configurational assignment adjacent of hydroxy/alkoxy- substituted carbons into chlorosulflipid.[1]

This approach also provides important imformations about their solution structures.

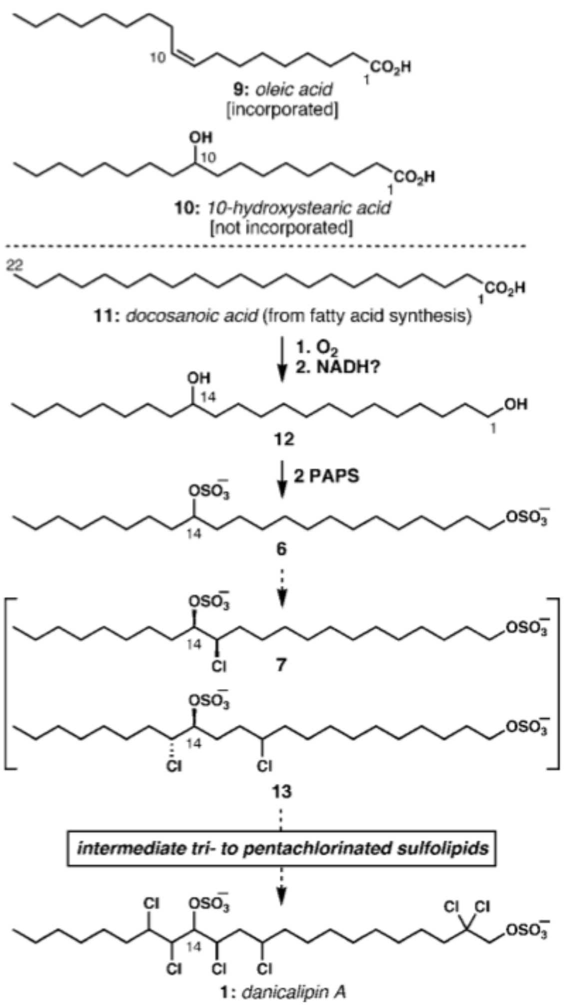
1. C. Nilewski, R. W. Geisser, M.-O. Ebert and E. M. Carreira, *J. Am. Chem. Soc.*, 2009, 131, 15866–15876.

Biosynthesis and biological relavance

Haines group demonstrated that the hydrocarbon chain is first constructed *via* the normal fatty acid biosynthetic pathway, and later functionalized with the polar substituents.

Enzyme-mediated transfer of the sulfate group of PAPS to the diol was postulated to be the final step in the biosynthesis of sulfolipid **6**.

Few details is known about the chlorination.
The chlorination is happened in **step-wise** fashion.
And it does not follow a **linear** path.
A new class of non-heme iron halogenases is found to be able to halogenate unactivated methyl group via **free-radical** process.

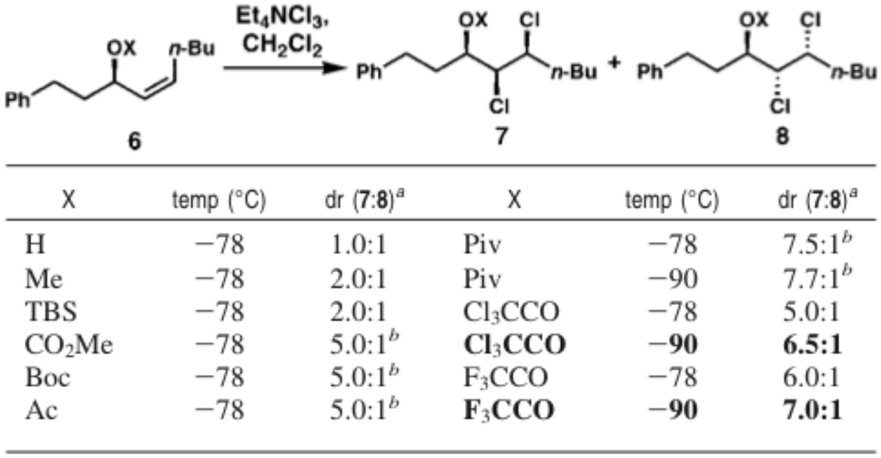


1. G. Thomas and E. I. Mercer, *Phytochemistry*, 1974, 13, 797–805.
2. J. Elovson, *Biochemistry*, 1974, 13, 3483–3487.
3. F. H. Vaillancourt, J. Yin and C. T. Walsh, *Proc. Natl. Acad. Soc.USA,* 2005, 102, 10111–10116.

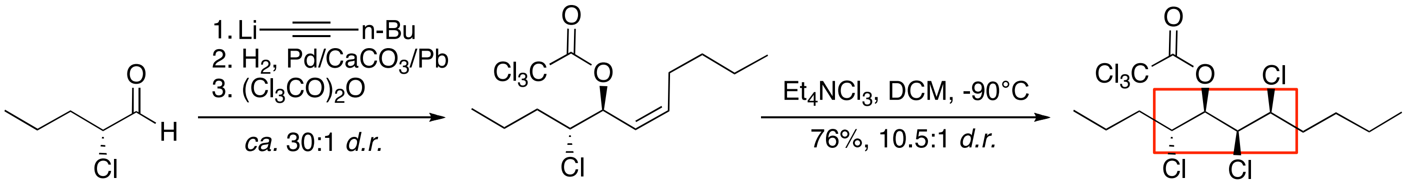
Vanderwal’s diastereoselective dichlorination

3 groups – Vanderwal’s, Carreira’s and Yoshimitsu/ Tanaka’s have been actively engaged in the development of methodologies and strategies for chlorosulfolipid synthesis in the past few years.

Dichlorination of (*Z*)-allylic trichloroacetates efficiently and stereoselectively generates the *syn*-*syn* hydroxydichloride.

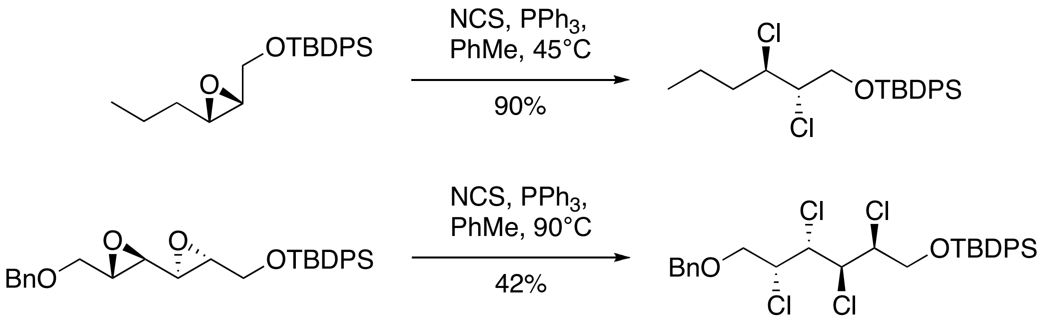


X	temp (°C)	dr (**7**:**8**)[a]	X	temp (°C)	dr (**7**:**8**)[a]
H	−78	1.0:1	Piv	−78	7.5:1[b]
Me	−78	2.0:1	Piv	−90	7.7:1[b]
TBS	−78	2.0:1	Cl_3CCO	−78	5.0:1
CO_2Me	−78	5.0:1[b]	**Cl_3CCO**	**−90**	**6.5:1**
Boc	−78	5.0:1[b]	F_3CCO	−78	6.0:1
Ac	−78	5.0:1[b]	**F_3CCO**	**−90**	**7.0:1**



1. G. M. Shibuya, J. S. Kanady and C. D. Vanderwal, *J. Am. Chem.Soc*., 2008, 130, 12514–12518.

Yoshimitsu/Tanaka deoxydichlorination of epoxide



The Yoshimitsu group expanded the use of **NCS/PPh$_3$** system to acyclic system.

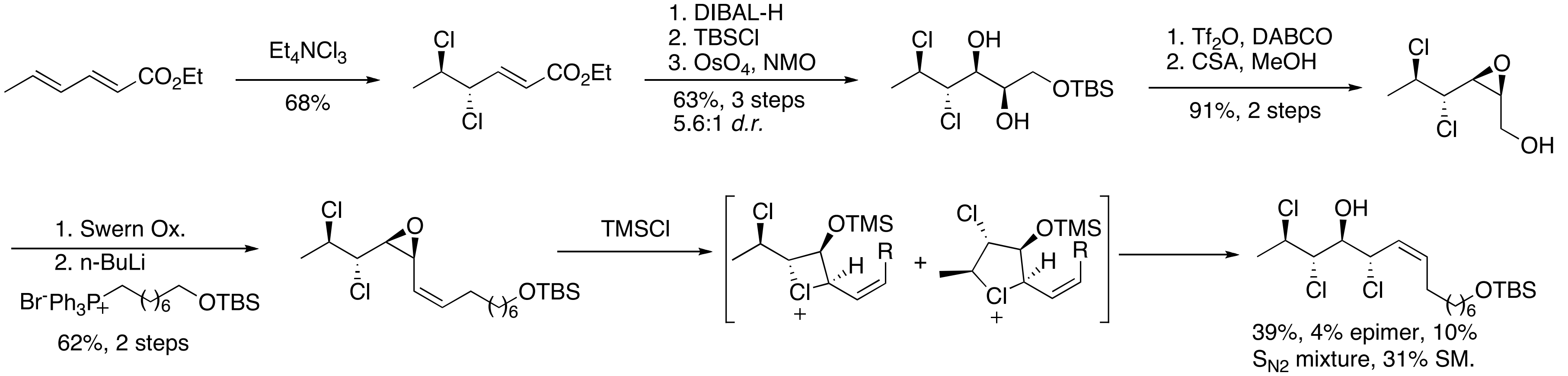
Their methodology included outstanding examples of stereospecific diepoxide to **tetrachloride** conversions.

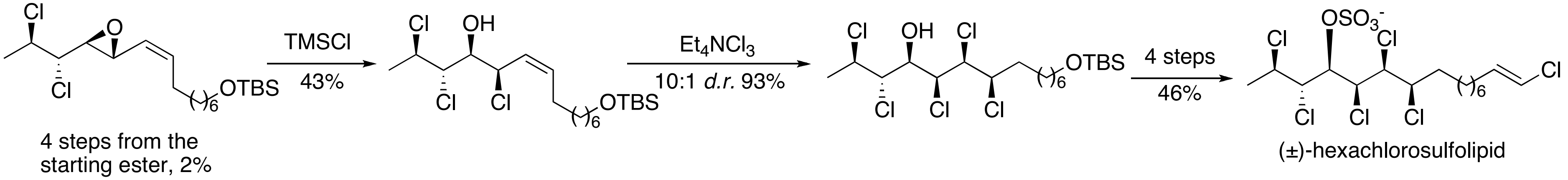
The combination of this reaction with the **Sharpless** asymmetric epoxidation of allylic alcohols presents a valuable entry into **enantioenriched polychlorides**.

These two methodologies provide important tools to approach the chlorosulfolipid.

1. T. Yoshimitsu, N. Fukumoto and T. Tanaka, *J. Org. Chem*., 2009, 74,696–702.

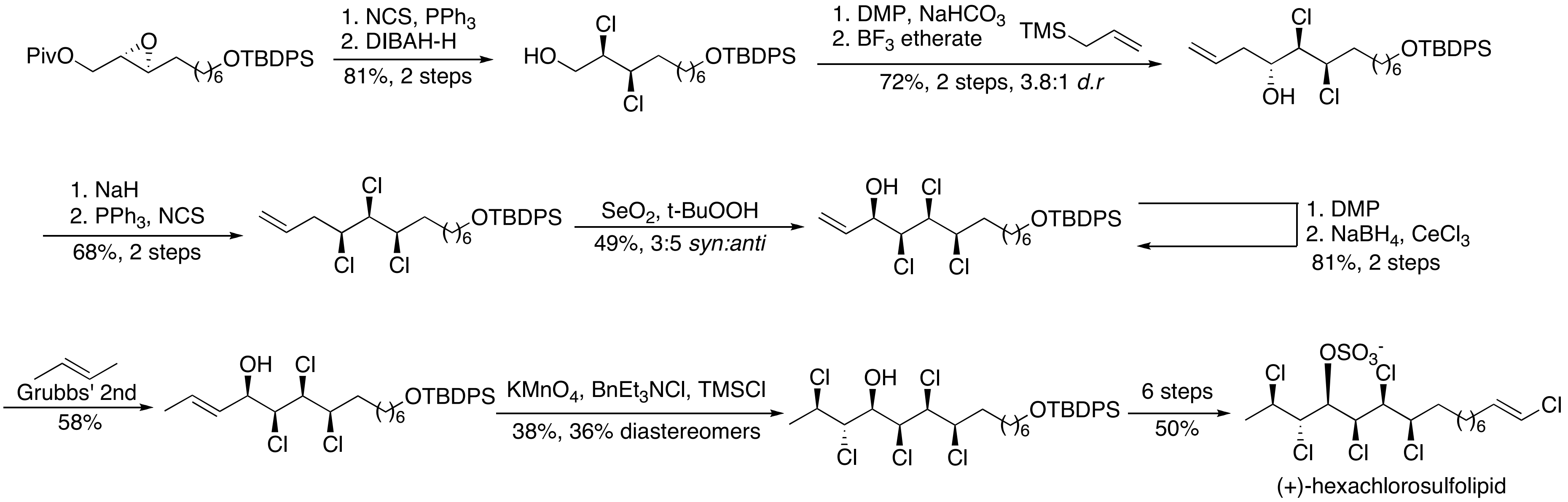
Carreira's synthesis of (±)-hexachlorosulfolipid





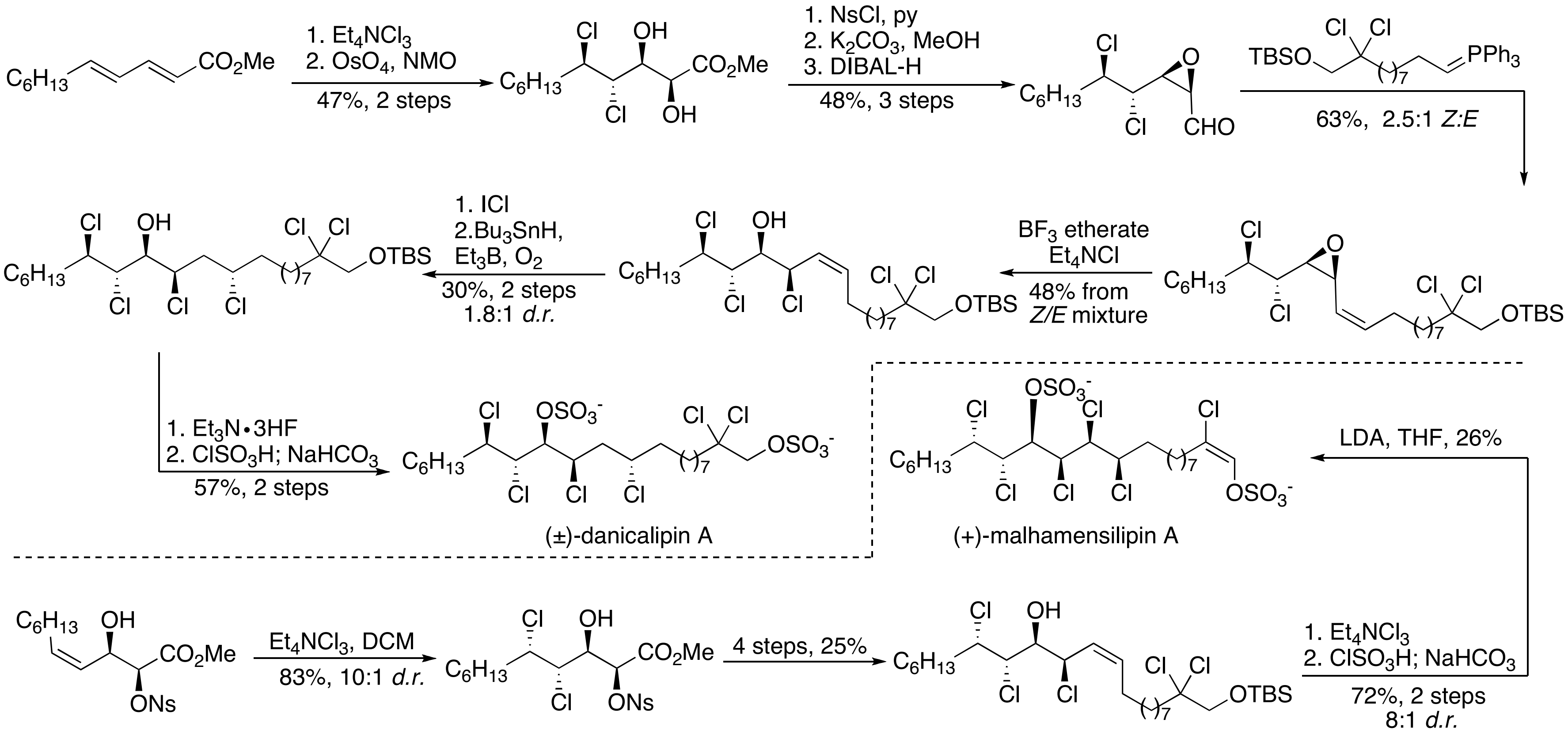
1. C. Nilewski, R. W. Geisser and E. M. Carreira, *Nature*, 2009, 457,573–577.

Yoshimitsu/Tanaka’s synthesis of (+)-hexachlorosulfolipid



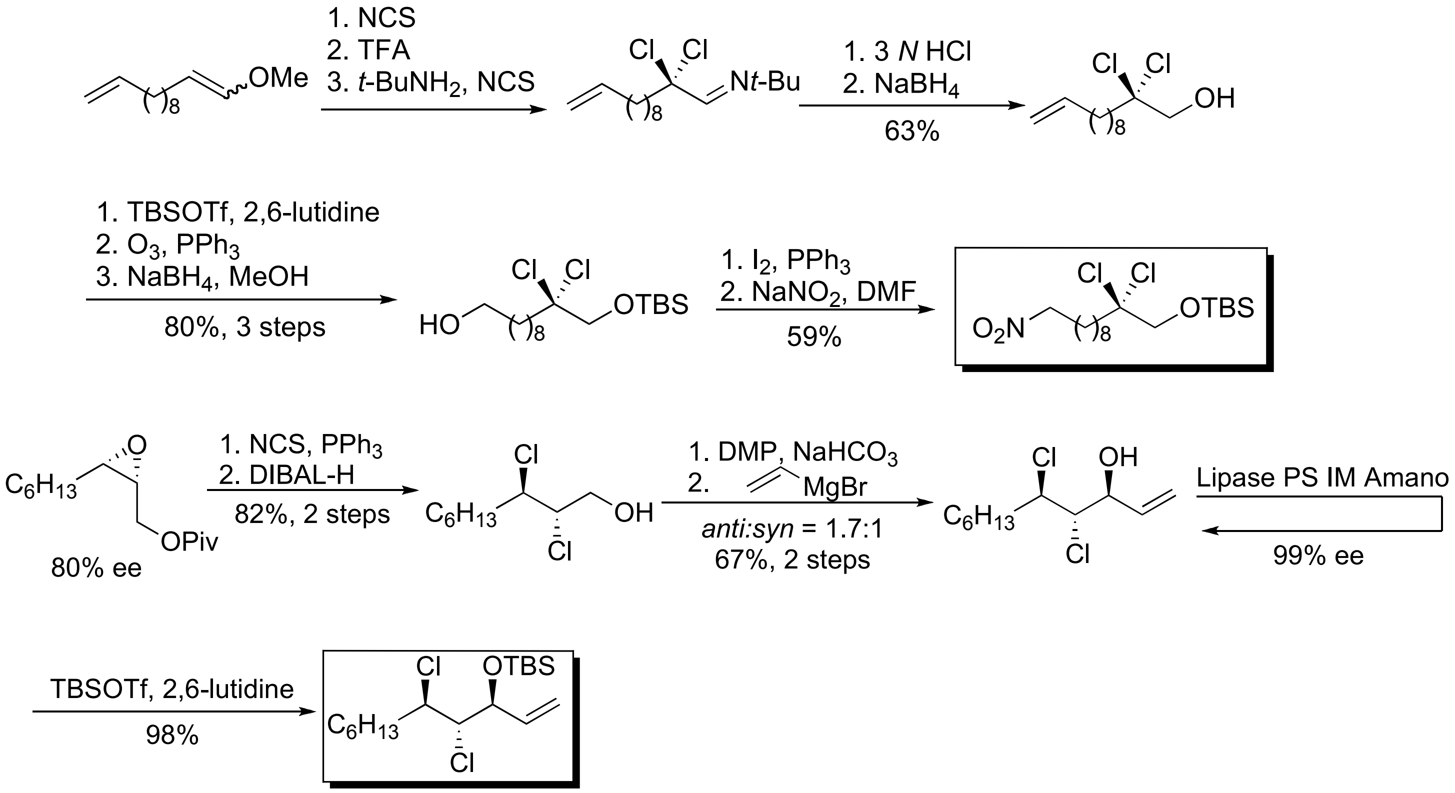
1. T. Yoshimitsu, N. Fujumoto, R. Nakatani, N. Kojima and T. Tanaka, *J. Org. Chem*., 2010, 75, 5425–5437.

Vanderwal’s total synthesis of chlorosulfolipid



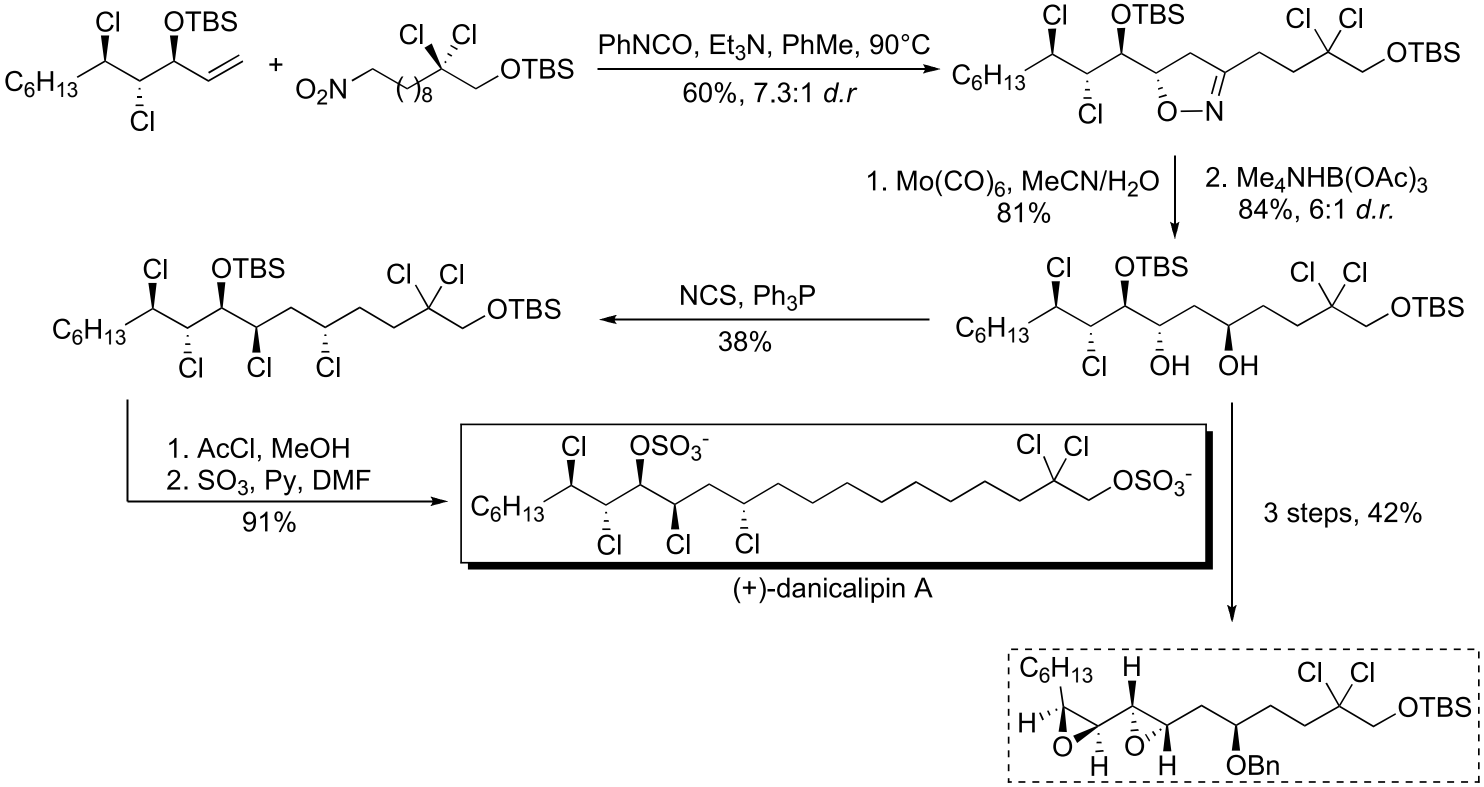
1. D. K. Bedke, G. M. Shibuya, A. Pereira, W. H. Gerwick, T. H.Haines and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2009, 131, 7570–7572.
2. D. K. Bedke, G. M. Shibuya, A. R. Pereira, W. H. Gerwick and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2010, 132, 2542–2543.

Title paper: total synthesis of (+)-danicalipin A



1. Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T. Org. Lett. ASAP

Title paper: total synthesis of (+)-danicalipin A



1. Yoshimitsu, T.; Nakatani, R.; Kobayashi, A.; Tanaka, T. Org. Lett. ASAP

Unanswered questions

The mechanism of **toxicity** of the mussel-derived lipid is unknown.

In *O. danica*, chlorosulfolipid is 90 mol% of its polar lipid and appeared to be very important component of **membrane**.

The mechanism of **chlorination** is poorly understand.

1. D. K. Bedke, C. D. Vanderwall, *Nat. Prod. Rep.*, 2011, 28, 15