Asymmetric Total Synthesis of (+)-Danicalipin A


Current literature
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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

In *Ochromonas 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.\(^2\)

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Elucidation of relative configuration of chlorosulfolipid

Carreira et al., applied Murata’s approach for the configurational assignment adjacent of hydroxy/alkoxy- substituted carbons into chlorosulfl lipid.¹

This approach also provides important informations about their solution structures.

Biosynthesis and biological relevance

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.

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.

<table>
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<th>dr (7.8)</th>
<th>X</th>
<th>temp (°C)</th>
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<tr>
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Yoshimitsu/Tanaka deoxydichlorination of epoxide

The Yoshimitsu group expanded the use of NCS/PPh₃ 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.

Carreira’s synthesis of (±)-hexachlorosulfolipid

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

Vanderwal’s total synthesis of chlorosulfolipid

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

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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.