"Halogen": derived from the Greek word meaning "salt-producing"  

1Natural Abundance of Halides/mg kg\(^{-1}\)  

<table>
<thead>
<tr>
<th>Halide</th>
<th>Oceans</th>
<th>Sedimentary Rock</th>
<th>Fungi</th>
<th>Wood Pulp</th>
<th>Plants</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(^-)</td>
<td>1.4</td>
<td>270-740</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl(^-)</td>
<td>19,000</td>
<td>10-320</td>
<td>70-2100</td>
<td>200-10,000</td>
<td></td>
</tr>
<tr>
<td>Br(^-)</td>
<td>65</td>
<td>1.6-3</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I(^-)</td>
<td>0.05</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each year, the oceans and volcanoes emit around 210 MT of chlorine equivalents into the atmosphere. HCl, NaCl\(^2\)  

Water: \(^1,3\)  
Ocean: nearly 2% Cl\(^-\) by weight; Great Salt Lake: 9% Cl\(^-\) by weight  
The enzymes in algae are able to more easily oxidize bromide, resulting in a higher occurrence of brominated secondary metabolites despite the higher concentration of chloride in the ocean.  

Terrestrial Environment: \(^1\)  
Halogens found in sediments, soils, plants, fungi, lichen, volcanoes, biomass combustion, bacteria, insects, and higher organisms.  

Peatlands: \(^1\)  
Wetlands with a thick water-logged organic soil layer composed of dead or decaying plant material and comprise 2% of the earth's surface.  
Major reservoir of organically bound iodine.  
91% of bromine found in peat is organically bound.  

Not surprisingly, many halogenated secondary metabolites originate from the ocean. These compounds have shown antimicrobial, antifeedant, antihelmintic, and cytotoxic activities and are increasingly being investigated as clinical targets.  

\(^1\) Gribble, G.W. Progress in the Chemistry of Organic Natural Products, 2010, 91, 613.  
\(^3\) The Chemistry of Halogens. http://chemed.chem.purdue.edu/
The Role of Halogen Bonding

1820s: Marks the emergence of halogenated drug candidates

Halides are used in place of hydrogen atoms in drug targets to make the molecules more lipophilic and hydrophobic i.e. they are better able to permeate lipid membranes and enter cells. As a negative result, they often accumulate in lipid (adipose) tissue.

Chlonidine: antihypertensive

Molecule efficacy can be largely influenced by orientation of substituents

Sterics: Halogens responsible for preventing rotation and positioning the rings in a perpendicular orientation

Halogen Bonding: "Occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity." The halogen acts as lewis acid while the Y is electron donating: R − X − − − Y

Advantages of Halogen bonding > hydrogen bonding

1) Halogen bonds are directional due to their narrowly confined σ-hole (region of positive electrostatic potential) on the outsersurface


3) Halogen bonds=hydrophobic. Hydrogen bonds=hydrophilic

4) The sheer size of halogens can alter the light-emitting properties of halogenated dyes by promoting singlet-to-triplet intercrossing.

"Specificity Pocket"

Aldose Reductase: enzyme responsible for the reduction of glucose to sorbitol. Long believed to be responsible for diabetic complications in various organs. Several aldose reductase inhibitors have been developed and withdrawn from the market due to toxicity effects resulting from off target inhibition of Aldehyde Reductase.

Solution: Halogen bonding.

Upon IDD 594 binding, Aldose Reductase undergoes a conformational change, creating a "specificity pocket." In this pocket, IDD 594 forms a halogen bond with Thr 113 at an unusually short bond length, contributing to the bonding specificity to aldose reductase. Aldehyde reductase contains a tyrosine moiety in place of the threonine and the increased steric bulky discourages non-specific binding.

---


There are discrepancies in the composition of halogenated drug candidates. The total halogen content in all drugs at Thomson Reuters Pharma is as follows:

- Fluorine: 20%
- Chlorine: 14.50%
- Bromine: 1.50%
- Iodine: 1.20%

Percentages include drugs containing multiple halogens. Source: Novartis, 2013.

The molecules in discovery stage represent the current opinions and interests in drug discovery, and the drug molecules in clinical phases represent the opinions and interests in drug discovery about a decade ago, while the launched phase collects the successful drugs over the past one hundred years.

Fluorine: commonly found as a trifluoromethyl substituent. Used in place of a chlorine atom or a methyl group at risk of metabolic oxidation. Also used to facilitate access to the CNS and transmission through the blood brain barrier.

Fluoxetine (Prozac)

Chlorine: provides increased lipophilicity, a source of hydrogen bonding, and a metabolic obstruction.

Loratadine (Claritin)

Bromine: less commonly used and mainly seen as a bromoaryl. Bromine can more easily generate alkylating intermediates than chlorine or fluorine, leading to toxicity issues (example: bromfenac, withdrawn from market).

Bromfenac

Iodine: Used by the body to produce thyroid hormones. KI is a treatment for deficiencies in hormone production. Organoiodide compounds are used as X-ray radiocontrast agents.

Diatrizoic acid

---

9 Vulpetti, A. "Protein interactions with fluorine and other halogens" Novartis, 2013
**Marine Organisms**

**Shenvi Lab Group Meeting**
2/1/16

**Samantha Green**

---

**Percentage of chlorinated or brominated secondary metabolites**

<table>
<thead>
<tr>
<th>Red Algae</th>
<th>Green Algae</th>
<th>Brown Algae</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>7%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Over 800 chlorinated and/or brominated forms of terpenes

The formation of organohalogenated compounds is thought to have developed in prokaryotes in response to the generation of reactive oxygen species (ROS). Similarly in algae, the halogenated compounds eliminate ROS while also playing a role in defense and structure maintenance.11

**Biosynthesis of methyl bromide/iodide**

Iodide and bromide are actively taken up from seawater and nucleophilically attack the CH$_3$S site of S-adenosylmethionine (SAM) halide/thiol methyltransferase. Limited to monohalogenation.

**Methylbromide formation**

![Methylbromide formation](image)

---

**Two classes of enzymes involved in halogenation:**

1) highly substrate-specific halogenases requiring dioxygen for enzymatic activity. Co-substrates: Flavin (FADH$_2$-dependent halogenases) or R-ketoglutarate (non-heme Fe$^{II}$/R-ketoglutarate/O$_2$-dependent halogenases).

2) less specific haloperoxidases (HPO) utilizing hydrogen peroxide (i.e. vanadium or heme hydroperoxidases).

In the 1980s, haloperoxidases were isolated from algae and the researchers were surprised to find stoichiometric quantities of vanadium rather than heme.

![Bound hypohalite (−OX) intermediates react as "X+" equivalents](image)

**Formation of α-, β-, and γ-Snyderol from Sesquiterpene Nerolidol**

![Formation of α-, β-, and γ-Snyderol from Sesquiterpene Nerolidol](image)

---

Vanadium dependent hydroperoxidases are named based on the most electronegative element they can oxidize. These enzymes are highly substrate non-specific.

The oxidation potential of the halides is pH-dependent, generally requiring a higher pH to oxidize the more electronegative halides.¹¹

Brown algae VHPOs have a common ancestor to the VHPOs of red algae; however, as first observed in Laminaria digitata, the brown algae developed novel biochemical function of iodine oxidation.

VIPOs are upregulated after an oxidative burst to restore iodine levels while VBrPOs are specifically activated and play a role in oxygen detoxification.

Laminaria digitata: approximately 1% iodide by dry weight. The kelp contains a 30,000 fold accumulation of iodide compared to seawater.

Iodide is thought to be stored via chelation with apoplastic macromolecules. This ensures abundant and readily accessible reduced iodine. However, the mechanism is not yet confirmed.

These iodine and bromine containing secondary metabolites primarily play a role in oxygen detoxification (quenching excess H₂O₂ and ROS) and bioadhesion; but also act in an antibacterial role on the kelp exterior.

Secondary Metabolites from Brown Algae:
Phlorotannins and Phloroglucinol

Biosynthesis with hydroxylation at the meta position are derived from the acetate-malonate pathway (additionally a PKS-type enzyme complex (?)). The triketide formed after cyclization undergoes tautomerization to give phenol. VHPOs shown to crosslink the monomers in vitro. Sulfated polyphenols are common in brown algae; but sulfur and halogen-substituted phenols have yet to be reported.

Halogenated Terpenes

Presense of terpenes is far more rare in brown algae than red, most likely due to red algae's ability to diversify their defense strategy.

Secondary metabolites from brown algae have not yet found a clinical use.

"The fact that some of the newly found halogenated compounds show minor or no activity at all against a specific target does not exclude the possibility of other hidden unidentified active biological effects."¹³

¹³ Cabrita, M.T. et al. Mar. Drugs 2010, 8, 2301-2317
Red Algae are the largest source of halogenated secondary metabolites. Specifically, *Laurencia* (shown right) is considered one of the most prolific. Diterpenes, sesquiterpenes, triterpenes, and C15-acetogenins are the main natural products and have been shown to have antimicrobial, antifeedant, anthelmintic, and cytotoxic properties.

**Various Isolated Compounds:**

- **Elatol:** Potent antibacterial
  - Isolated from *Plocamium cornutum.* 
  - IC₅₀ = 16 µM against Plasmodium falciparum (most deadly human malaria parasite)

- **Hamigrene subclass of sesquiterpenes**

- **Bromphycolide active against *S. aureus* and cytotoxic but showed little cell line selectivity**

- **Ambiguine M**

- **Isolated from cyanobacteria. Potent activity against Mycobacterium tuberculosis.**

- **Securamine G**
  - Isolated from *bryozoans S. securifrons.*
  - Not apparent that there's biological activity from this scaffold. In different variants of this scaffold, they exist in equilibrium with securine dependent on solvent (DMSO-d₆ vs CDCl₃).

- **Psammopemmin B**
  - Isolated as the amine salt from Antarctic marine sponge *Psammopemma sp.* Suspected to have pharmacological activity due to the 4-hydroxyindole but the isolated quantity was too little for bio testing. Still awaiting structure confirmation via total synthesis.

- **Aplicyanin F**

- **Meridianin B**

- **Meridianin E**
  - The two most potent of the family. Activity: inhibition of various protein kinases (protein phosphorylation) and cytotoxicity LMM3 (murine mammalian adenocarcinoma cell line)
  - IC₅₀ of 11.4 µM and 11.1 µM

- **Psammopemmin B**

**This is by no means a complete list of available methods**

**Appel Reaction**

\[
\text{OH} \quad \xrightarrow{\text{CX}_4, \text{PPh}_3} \quad \text{X} \quad \xrightarrow{} \quad \text{primary or secondary alcohols inversion of stereochemistry}
\]

Tertiary Alcohols: Strong acid (HCl, HI, HBr)
Primary/Secondary Alcohols: various methods of S_n2: SOCl_2, SOBr_2, PBr_3, PCl_3, PCl_5, PBr_5, MsCl/EtN_3 (can directly replace with chlorides in some substrates) or TsCl/pyridine and then nucleophilic substitution with halide.

**Finkelstein Reaction** (alcohol or halide displacement)

\[
R^1 \xrightarrow{\text{NaX}^2 \text{ or LIX}^2} \quad R^2 \quad \text{Inversion of stereochemistry} \\
X^1 = \text{F, Cl, Br, I, OMs, OTs} \\
\text{Constrained by solubility of the sodium or lithium halide}
\]

**Hunsdiecker Reaction**

\[
\text{R}^1 \xrightarrow{\text{O}^- \text{Ag}^+} \quad \text{R}^2 \quad \text{Br}_2 \xrightarrow{\text{CCl}_4} \quad \text{R}-\text{Br} \\
\text{Radical mechanism for the formation of alkyl or aryl halides}
\]

Modifications:
1) Thallium(I)-carboxylates instead of silver salts
2) Cristol-Firth modification- excess red HgO and one equivalent of halogen
3) Suarez modification- treatment of acid with hypervalent iodine in CCl_4
4) Kochi modification- Pb(OAc)_4 with iodine or lithium halide
5) Barton modification- thermal of photolytic decomposition of thiohydroxamate esters in halogen donor solvents
6) AIBN can decarboxylate aromatic acids

**Wohl-Ziegler Bromination**

\[
\text{R}^1\text{CH}_2\text{R}^2 + \text{O}^\text{Br} \quad \xrightarrow{\text{radical initiator}} \quad \text{Br}_{\text{R}^1\text{CH}_2\text{R}^2} \\
\text{heat or h}_\nu
\]

**Balz-Schiemann Reaction**

\[
\text{Ar-NH}_2 \quad \xrightarrow{\text{HNO}_2/\text{HBF}_4} \quad \text{Ar-} \quad \xrightarrow{\Delta} \quad \text{Ar-F}
\]

**Ciamician-Dennstedt Rearrangement**

\[
\text{CHX}_3 \quad \xrightarrow{\text{strong base}} \quad \text{Nucleophile addition} \\
\text{strong base}
\]

**Hell-Volhard-Zelinsky reaction**

\[
\text{R}^1\text{CH}_2\text{R}^2 \quad \xrightarrow{\text{X}_2 \text{P or PX}_3} \quad \text{R}^1\text{CH}_2\text{R}^2 \\
\text{H}_2\text{O} \quad \xrightarrow{\Delta} \quad \text{R}^1\text{CH}_2\text{R}^2 \\
\text{Nuc-H} \quad \xrightarrow{\Delta} \quad \text{R}^1\text{CH}_2\text{R}^2 \\
\text{Nuc}
\]

**Sandmeyer Reaction**

\[
\text{PhNH}_2 \quad \xrightarrow{\text{NaNO}_2/\text{HX}} \quad \text{Ph-} \quad \xrightarrow{\text{Cu}^{(I)}X} \quad \text{Ph-}
\]

---

15Czako B., Kurti, L. *Strategic Applications of Named Reactions in Organic Synthesis.*
Methods of Halogen Insertion in Synthesis

Shenvi Lab Group Meeting
2/1/16

Samantha Green

C-H aliphatic Bromination

Hofmann-Loffler-Freytag Reaction

\[ \text{R}^1 \text{N}^{\text{X}} \text{R}^2 \xrightarrow{\Delta \text{or } \text{hv} \text{ or radical initiator}} \text{R}^1 \text{N}^{\text{H}} \text{R}^2 \]

Nitrogen-centered radica to do site-selective, intramolecular C-H functionalizations

Erik Alexanian, JACS 2014\(^{16}\)

\[ \text{Me} \xrightarrow{\text{Br}} \text{Me} \]

\[ \text{PhthN} \xrightarrow{\text{Br}} \text{PhthN} \]

1 equiv 1 equiv

- Reactions run with a 100 W household lightbulb.
- Run under Ar; however, little decrease in yield when run under air
- No dihalogenation observed (electronic deactivation of bromoalkane pdt)

\[ \text{F}_3\text{C} \text{O}^{\text{N}} \text{tBu} \xrightarrow{\text{Br}} \text{F}_3\text{C} \text{Cl} \]

Provided the highest yields (75\%, 98.5\% selective for 2\(^{\circ}\) to 3\(^{\circ}\) bromination). Favors tertiary bromination with adamantane. In other cases though, highest selectivity for methylene yet reported.

C-H aliphatic Chlorination

Vanderwal and Alexanian, JACS 2015\(^{17}\)

Chlorine free radicals are far more promiscuous than bromine. Bromine is often site-selective for the weakest C-H bond while chlorine undergoes polyhalogenation and poor site selectivity.

\[ \text{Cs}_2\text{CO}_3, 55^\circ \text{C}, \text{hv} \]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>% selectivity of chlorination</th>
<th>total yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>(\beta)</td>
<td>(\gamma)</td>
</tr>
<tr>
<td>EWG-(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. PhthN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. NC</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. Cl</td>
<td>9.2</td>
<td>5.7</td>
</tr>
<tr>
<td>4.</td>
<td>23.9</td>
<td>65.5</td>
</tr>
</tbody>
</table>


Methods of Halogen Insertion in Synthesis

Shenvi Lab Group Meeting 2/1/16

Vanderwal and Alexanian, JACS 2015 (cont.)

<table>
<thead>
<tr>
<th>entry</th>
<th>major chlorination product</th>
<th>% select.</th>
<th>Total yield (%)</th>
<th>sites of minor chlorination (% selectively)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PhthNCl&lt;sub&gt;α&lt;/sub&gt;Cl&lt;sub&gt;δ&lt;/sub&gt;Cl&lt;sub&gt;ε&lt;/sub&gt;</td>
<td>63.6</td>
<td>69</td>
<td>β=2.4; γ=7.5; ε=26.5</td>
</tr>
<tr>
<td>2.</td>
<td>PhthNCO&lt;sub&gt;2&lt;/sub&gt;MeCl&lt;sub&gt;α&lt;/sub&gt;Cl&lt;sub&gt;δ&lt;/sub&gt;</td>
<td>77.5</td>
<td>66</td>
<td>ε=26.5</td>
</tr>
<tr>
<td>3.</td>
<td>PhthNCl&lt;sub&gt;α&lt;/sub&gt;Cl&lt;sub&gt;δ&lt;/sub&gt;Ph</td>
<td>67.9</td>
<td>81</td>
<td>γ=14.9; ε=17.2</td>
</tr>
<tr>
<td>4.</td>
<td>PhthNCl&lt;sub&gt;α&lt;/sub&gt;Cl&lt;sub&gt;δ&lt;/sub&gt;allenyl</td>
<td>74.0</td>
<td>78</td>
<td>α=6.5; ε=18.9</td>
</tr>
<tr>
<td>5.</td>
<td>MsO&lt;sub&gt;α&lt;/sub&gt;Cl&lt;sub&gt;δ&lt;/sub&gt;alkene</td>
<td>100</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Application in synthesis of (+)-Chlorolissoclimide

1. CH<sub>3</sub>ONHCH<sub>2</sub>·HCl, Al(CH<sub>3</sub>)<sub>3</sub>, THF (91%)
2. SOCl<sub>2</sub>, pyr. (76%)

(+)-sclareolide

1. 2 (equiv), hv, Cs<sub>2</sub>CO<sub>3</sub>, PhH, 55°C (82%)

(+)-chlorolissoclimide

1. CH<sub>3</sub>ONHCH<sub>2</sub>·HCl, Al(CH<sub>3</sub>)<sub>3</sub>, THF (91%)
2. SOCl<sub>2</sub>, pyr. (76%)

(+)-chlorolissoclimide
**Chlorosulfolipids**

Molecule significance:
1) allow for confirmation of stereochemistry
2) One has been found to be a protein kinase inhibitor (no given IC data)
3) Synthetic challenge
4) "electronically distinct isosteres of polyketide natural products." polyketides are pharmacologically relevant so maybe these are too...?

\[
\begin{align*}
\text{1 mytilipin A (hexachlorosulfolipid)} & : \quad \text{ClOSO}_3^- \\
\text{n-C}_{15}H_{31} & : \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
\text{2: } X = \text{H mytilipin B} & \\
\text{3: } X = \text{OH mytilipin C} & \\
\text{4: (±)- danicalipin A} & : \quad \text{ClOSO}_3^- \quad \text{Cl} \\
\text{5: malhamensilipin A} &
\end{align*}
\]

Studies into the biosynthesis reveal that the hydrocarbon chain is constructed via the normal fatty acid biosynthetic pathway and subsequently functionalized with the polar substituents. The biosynthesis of the chlorination is unknown. The chlorides reside on unactivated carbons, so it is unlikely to be electrophilic sources of halogen. Less chlorinated lipids were resubjected to culture media containing chlorine sources and were further chlorinated.\(^{18}\)


\(^{20}\) Denmark, S.E. et al. *Nat. Chem.*, 2015, 7, 146-152.
Shenvi, JOC 2009\textsuperscript{21} Deoxydichlorination of epoxides

\[
\text{[OTBDPS]} \xrightarrow{\text{ObN, O}_{2}} \text{Cl-OTBDPS} \quad (90\% \text{ yield})
\]

\[
\text{[OTBDPS]} \xrightarrow{\text{NCS, PPh}_3^-, \text{PhMe, 45°C}} \text{Cl-OTBDPS} \quad (42\% \text{ yield})
\]

Total Synthesis of mytilipin A (hexachlorosulfolipid)

Carreira, Nature 2009\textsuperscript{22}

\[
\text{Me}-\text{CO}_2\text{Et} \xrightarrow{\text{(H}_2\text{C}_2\text{)NCI}_2^-, \text{CH}_2\text{Cl}_2, 0°C} \xrightarrow{\text{DIBAL (2.3 equiv), H}_2\text{C}_2\text{H}_2\text{O}, 0°C} \xrightarrow{\text{NMO (1.1 equiv), TPAP (5 mol%), CH}_2\text{Cl}_2} \xrightarrow{\text{m-CPBA, CH}_2\text{Cl}_2, 0°C→RT} \xrightarrow{\text{(H}_2\text{C}_2\text{)NCI}_2^-, \text{CH}_2\text{Cl}_2, -78°C} \xrightarrow{\text{(d.r.}=1:1, 95\% \text{ overall})} \xrightarrow{\text{R}=\text{TBS}} \xrightarrow{\text{Cl}} \xrightarrow{\text{BrPh}_3^+, \text{OTBS}} \xrightarrow{\text{(H}_2\text{C}_2\text{)SiCl} (2 \text{ equiv), CH}_2\text{Cl}_2, \text{H}_2\text{CCO}_2\text{C}_2\text{H}_5} \xrightarrow{(43\%)} \xrightarrow{(d.r.}=1:1, 93\% \text{ overall})} \xrightarrow{\text{R}=\text{Me}}
\]

Comments: Initial route used the cis epoxide in place of trans. During the first route, they assumed that chlorohydrin diastereomer after epoxide opening had a syn relative configuration and proceeded to the end. When the natural product NMR did not match the isolated NMR, they reassess the configuration, realizing the epoxide opening gave anti-selectivity. The trans epoxide gave similarly anti-configuration and they were able to proceed with this new route. The anti-configuration is thought to occur due to anchimeric participation of one of the chlorides at C2 and C3 during the ring opening.

TPAP=tetra-\text{-}n\text{-propylammonium} \text{ perruthenate(VII)}


Chlorosulfolipids

Vanderwal, Angew. Chem. 2013

\[ \text{OH} \quad \text{Cl}_2, \text{Et}_4\text{NCl}, \text{CH}_2\text{Cl}_2, 0^\circ \text{C} \quad (89\%) \]

Dess-Martin periodinane

\[ \text{Br} \quad \text{AlEt}_2 \]

1. Mg, THF, then DMF (65%)
2. CrCl_2, CHCl_3 (79%, 93:7 E/Z)

\[ \text{Cl} \quad \text{Br} \quad \text{Cl} \]

NaOH, Et_4NCl, H_2O (52% 2 steps 98:2 d.r.)

\[ \text{Cl} \quad \text{O} \quad \text{Cl} \]

SiCl_4, Denmark cat. (20 mol%), Pr_2NEt, CH_2Cl_2 (43% isolated 93.5:6.5 d.r)

(R,R)-dimeric Denmark catalyst

1. Mg, THF, then DMF (65%)
2. CrCl_2, CHCl_3 (79%, 93:7 E/Z)

\[ \text{Cl} \quad \text{O} \quad \text{Cl} \]

Ar, DCE/CH_2Cl_2, 35°C (32%, >20:1 Z/E)

\[ \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \]

(325 mol%, Grubbs catalyst (1))

Ar, DCE/CH_2Cl_2, 35°C (32%, >20:1 Z/E)

\[ \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \]

(86% 97:3 d.r.)

\[ \text{Cl} \quad \text{O} \quad \text{Cl} \]

BF_3•OEt_2, Et_4NCl (72%)

Comments: longest linear is 7 steps, overall 9% yield, prepared over 100 mg. Enantioselective synthesis is 8 steps longest linear ((+)-mytilipin A after kinetic resolution).

(+)-hexachlorosulfolipid

\[ \text{SO}_3^\text{-py} \]

(94%)

\[ \text{R}=\text{H} \quad \text{R}=\text{SO}_3^- \]

Yoshimitsu, JOC 2010

1) Sharpless Asym. Expoxidation
2) PivCl, Et₃N, CH₂Cl₂, rt
   (99% for 2nd step, no yield for 1)

1) Dess-Martin
   NaHCO₃, CH₂Cl₂
   (70%)

1) Ac₂O, Et₃N, DMAP
   CH₂Cl₂, rt. (quat)
2) aq. HF/pyridine
   THF, (94%)
3) Dess-Martin
   CH₂Cl₂, rt, (98%)
4) CrCl₂, CHCl₃
   THF, 65°C, (75%)
5) DIBAL, CH₂Cl₂
   −78°C, (96%)
6) SO₃⁻ Pyridine
   DMF, rt, (75%)

2) NaBH₄,
   CeCl₃•7H₂O
   MeOH, 0°C
   (81% 2 steps)

Dihalogenation of Alkenes

Problems with dibromination:
1) Racemization of chiral bromonium ions in the presence of alkenes (Denmark).
2) Regioselectivity during bromide addition for stereocontrol of the product.

First general method for the enantio- and regioselective addition of two different halogen atoms across alkene

HO-\text{Ph} + \text{NBS} \rightarrow \text{HO-Ph} - \text{Cl} + \text{HO-Ph} - \text{Br}

<table>
<thead>
<tr>
<th>Entry</th>
<th>conditions</th>
<th>yield A + B</th>
<th>A:B</th>
<th>ee A,B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyr•HCl instead of ClTi(O-i-Pr)_3</td>
<td>80</td>
<td>1:4</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CH_2Cl_2, r.t.</td>
<td>85</td>
<td>1:2</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>50 mol %, 1, CH_2Cl_2, r.t.</td>
<td>88</td>
<td>1:2</td>
<td>6,8</td>
</tr>
<tr>
<td>4</td>
<td>50 mol %, 2, CH_2Cl_2, r.t.</td>
<td>73</td>
<td>1:2</td>
<td>12,6</td>
</tr>
<tr>
<td>5</td>
<td>50 mol %, 3, CH_2Cl_2, r.t.</td>
<td>89</td>
<td>1:1</td>
<td>17,0</td>
</tr>
<tr>
<td>6</td>
<td>50 mol %, 4, CH_2Cl_2, r.t.</td>
<td>67</td>
<td>1:1</td>
<td>63,6</td>
</tr>
<tr>
<td>7</td>
<td>50 mol %, 4, hexanes, r.t.</td>
<td>70</td>
<td>8:1</td>
<td>94,52</td>
</tr>
<tr>
<td>8</td>
<td>50 mol %, 4, hexanes, -20°C</td>
<td>80</td>
<td>&gt;20:1</td>
<td>98,−</td>
</tr>
<tr>
<td>9</td>
<td>10 mol %, 4, hexanes, -20°C</td>
<td>88</td>
<td>&gt;20:1</td>
<td>94,−</td>
</tr>
</tbody>
</table>


**Plocamium Monoterpenes**

*Plocamium*, a species of red algae, is a prolific source of halogenated monoterpenes, both cyclic and acyclic. Halomon shows cytotoxicity against chemotherapy-resistant cell lines (renal, brain, colon, non-small-cell lung). Overall, the family seems promising for their cytotoxic potential.

**Chemical Structures**

- (+)-halomon
- (E)-plocamenone
- (Z)-isoplocamenone

**Synthesis**

1. **1) NaIO₄**
   - 5 mol% aq. NaHCO₃
   - 0°C→r.t.

2. **2) Ph₃P=CO₂Et**
   - CH₂Cl₂, 0°C
   - (91%)

- **TFAA/pyr, then Et₄NCl₃, then NH₄OH/MeOH**
  - (66%, 6:1 d.r.)

- **(94%) Dess-Martin**
  - R=H
  - R=CHO

- **Ph₃P=CHBr**
  - (63%, 10:1 Z/E)

- **Ph₃P=CH₂**
  - (88%)
(-)-Plocamenone and (-)-Isoplocamenone

NBS
ClTi(Oi-Pr)₃,
20 mol% (S,R)-1
hexanes, −20°C

(64%, 95% ee)

1) Dess-Martin
NaHCO₃, CH₂Cl₂, r.t.

2) 2, NaHMDS
THF, −78→0°C
(70% 2 steps
Z/E=13:1)

(E)-(−)-plocamenone

1) TMSOTf, i-Pr₂NEt;
3, −78→r.t.

2) MeI, i-Pr₂NEt
THF, rt
(54% 2 steps)

(Z)-(−)-isoplocamenone

NBS
ClTi(Oi-Pr)₃,
20 mol% (R,S)-1
hexanes, −20°C

(73%, 90% ee)

1) Tf₂O, 2,6-lut.
CH₂Cl₂, −78°C

2) L-Selectride,
THF, −78°C
(95% crude 2 steps)

(+)-halomon

1) Br₂, K₂CO₃
hexanes, −78°C
2) LiOAc, DMF, 0°C

3) K₂CO₃, MeOH
0°C→r.t.
(39% a, 22% b)