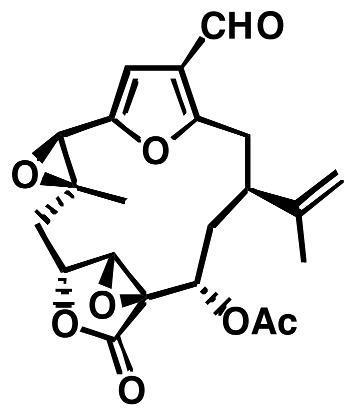
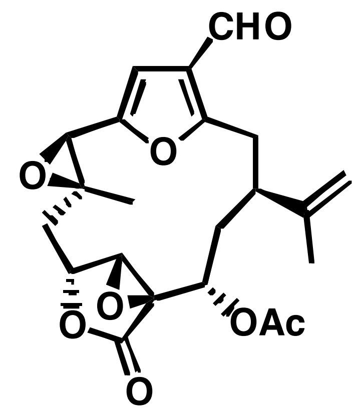
Progress towards the Total Synthesis of Lophotoxin



Michel Grenon

July 10th, 2004

Presentation Outline



☛ **Cell signaling between neurons**

Mechanism

Neurotransmitters and their protein receptors (ionotropic)

☛ **Lophotoxin**

Isolation and structural features

Other members of the furanocembranolides

Bioactivity

☛ **Lophotoxin (Synthetic work)**

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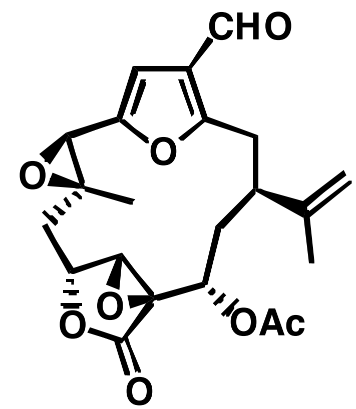

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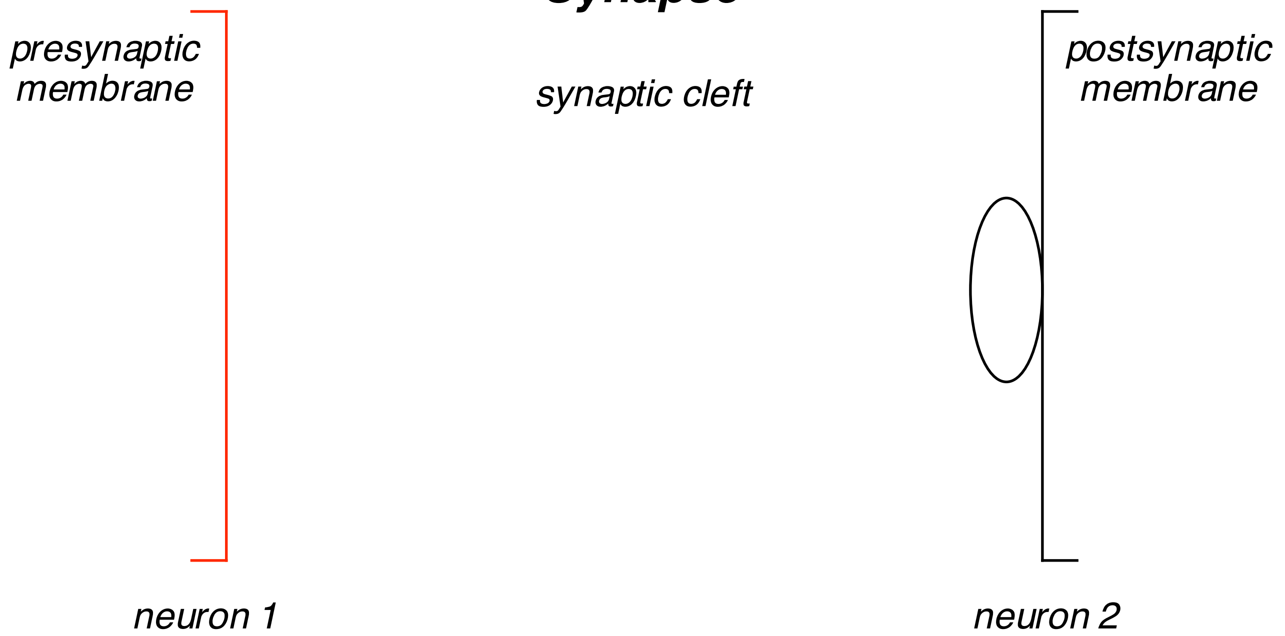
Mechanism of Cell Signaling in the Central Nervous System

The Central Nervous System (CNS) is composed of billions of neurons

The correct functioning of the CNS is based on the generation, propagation and coordinated integration of signals between different neurons

The communication between nerve cells is performed at a highly specialized region called the *Synapse*

Synapse



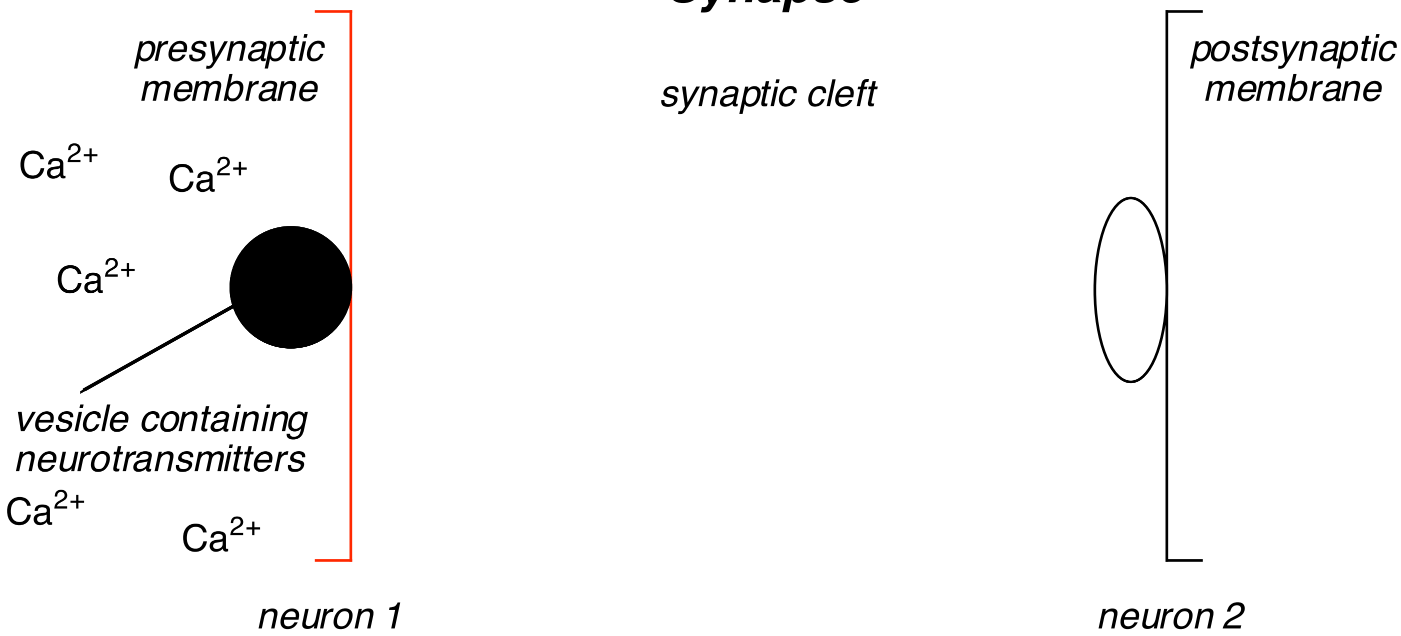
Mechanism of Cell Signaling in the Central Nervous System

The tranfer of information is achieved chemically by molecules called neurotransmitters

Membrane depolarization results in enhancement of Ca^{2+} permeation

At raised intracellular Ca^{2+} concentrations, vesicles containing neurotransmitters fuse with the presynaptic membrane

Synapse

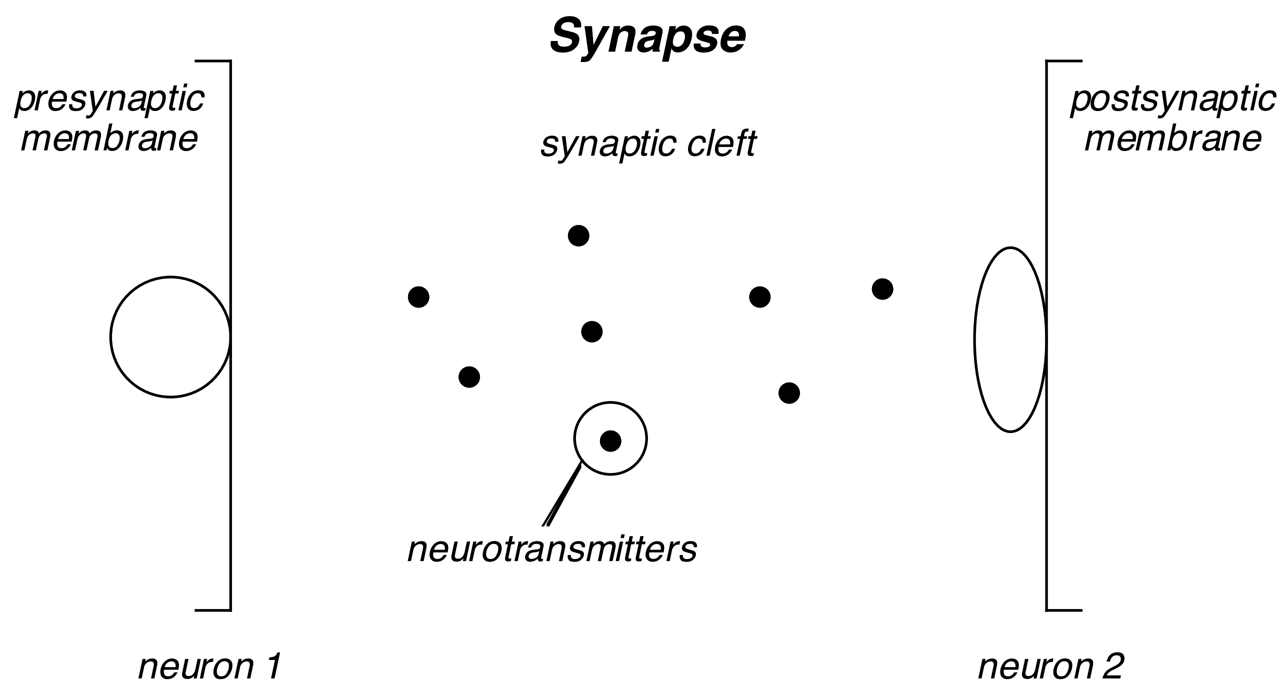


Mechanism of Cell Signaling in the Central Nervous System

The vesicle content is spilled into the synaptic cleft

The time course for neurotransmitter clearance is between 0.1 and 2.0 ms

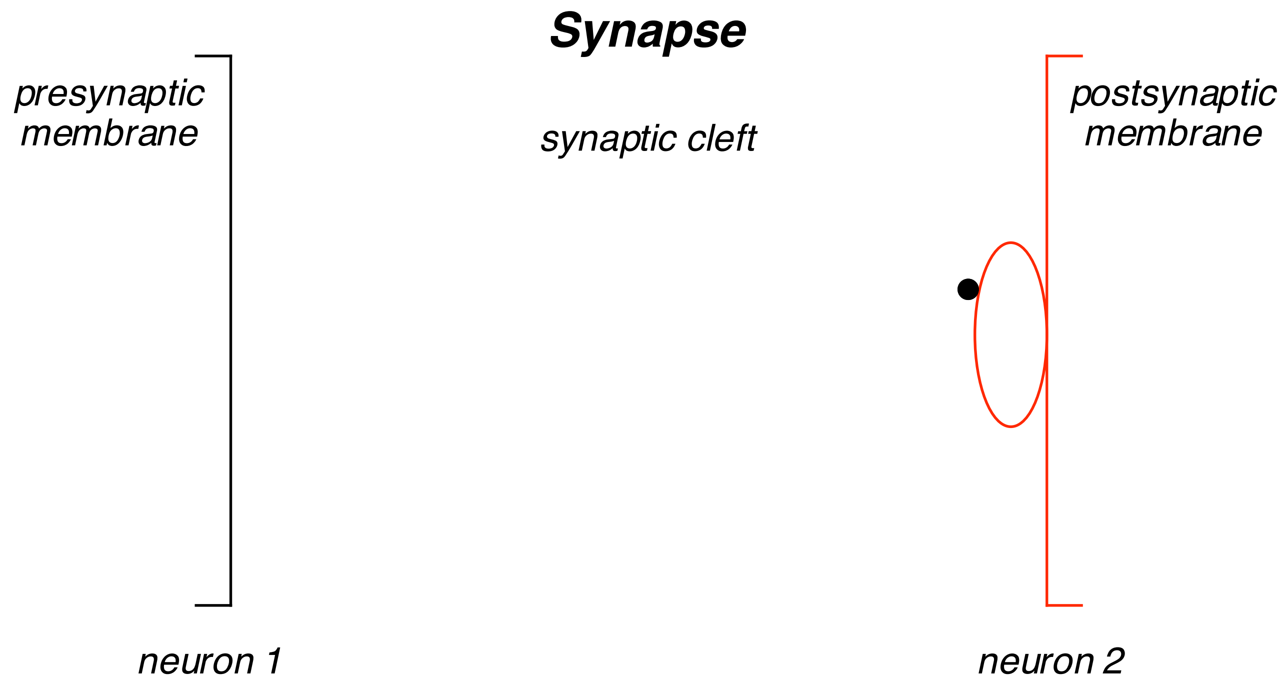
The neurotransmitter molecules diffuse through the synaptic space in less than 0.2 ms, reaching concentrations of 1-5 mM



Mechanism of Cell Signaling
in the Central Nervous System

The chemical information is converted into electrical currents on the postsynaptic membrane

This latter membrane is highly specialized in the recognition and binding of neurotransmitters by means of protein receptors

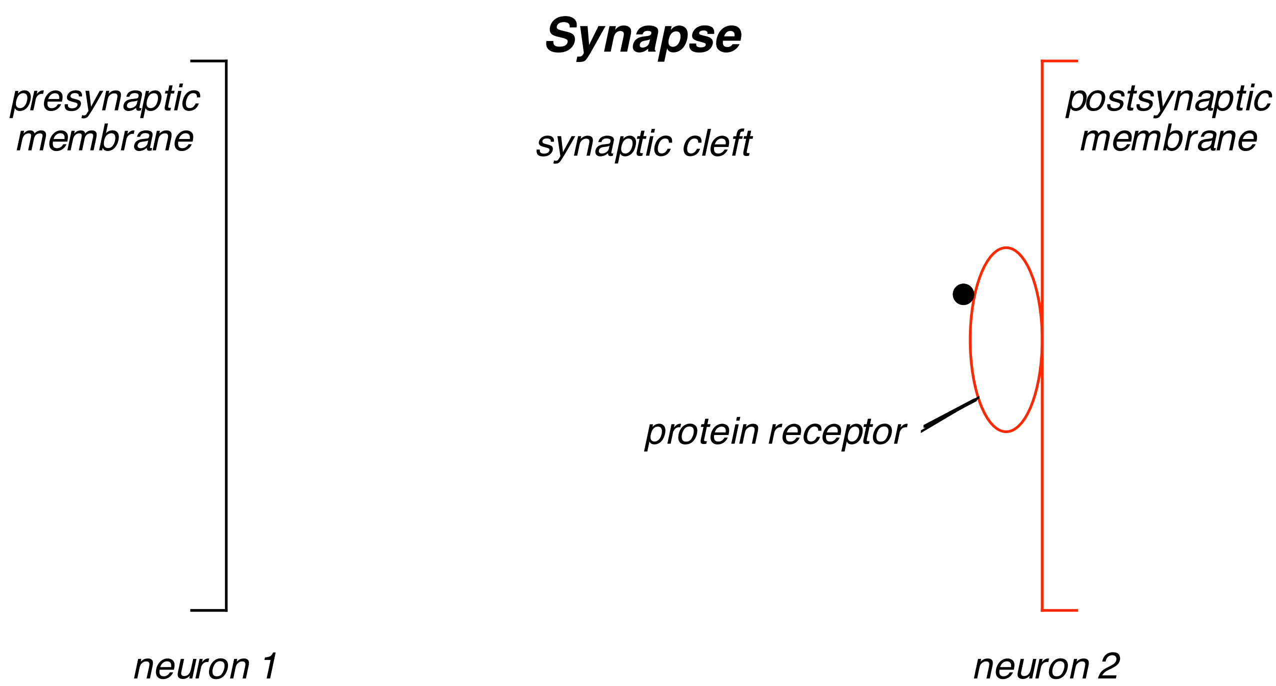


Mechanism of Cell Signaling in the Central Nervous System

The chemical information is converted into electrical currents on the postsynaptic membrane

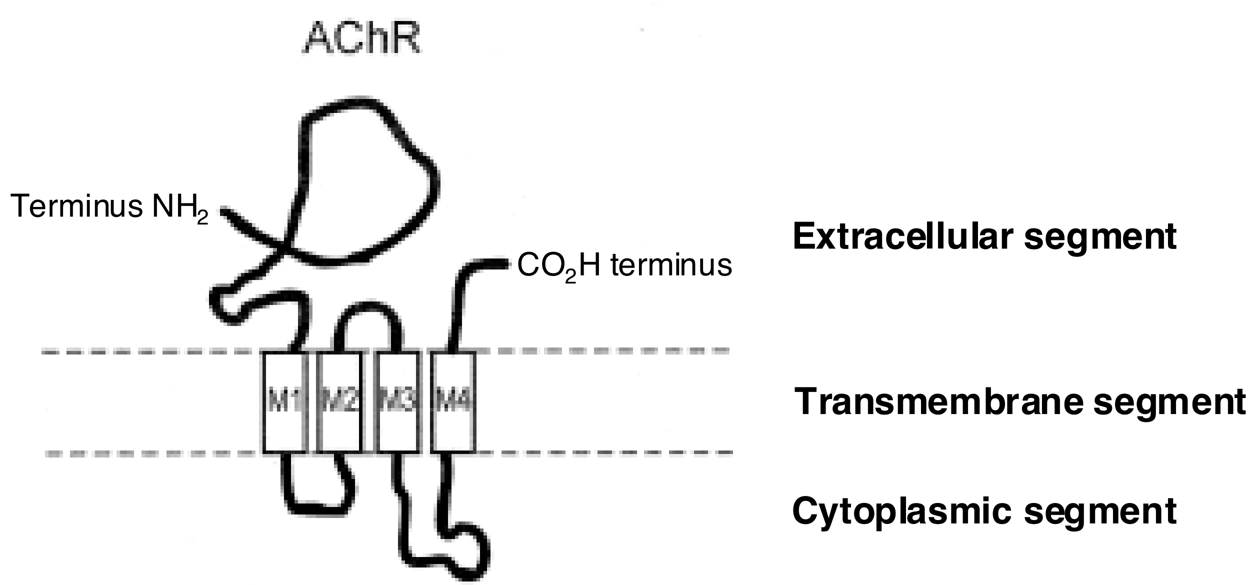
There are two main receptor classes; *ionotropic* and *metabotropic*

The binding of a neurotransmitter to its ionotropic receptor induces a fast opening of the ion channel (Na^+, K^+ or Ca^{2+}) intrinsically coupled to the receptor



Example of Ionotropic Receptor: Nicotinic Acetylcholine Receptor (AChR)

Diagram of the tertiary organization of AChR

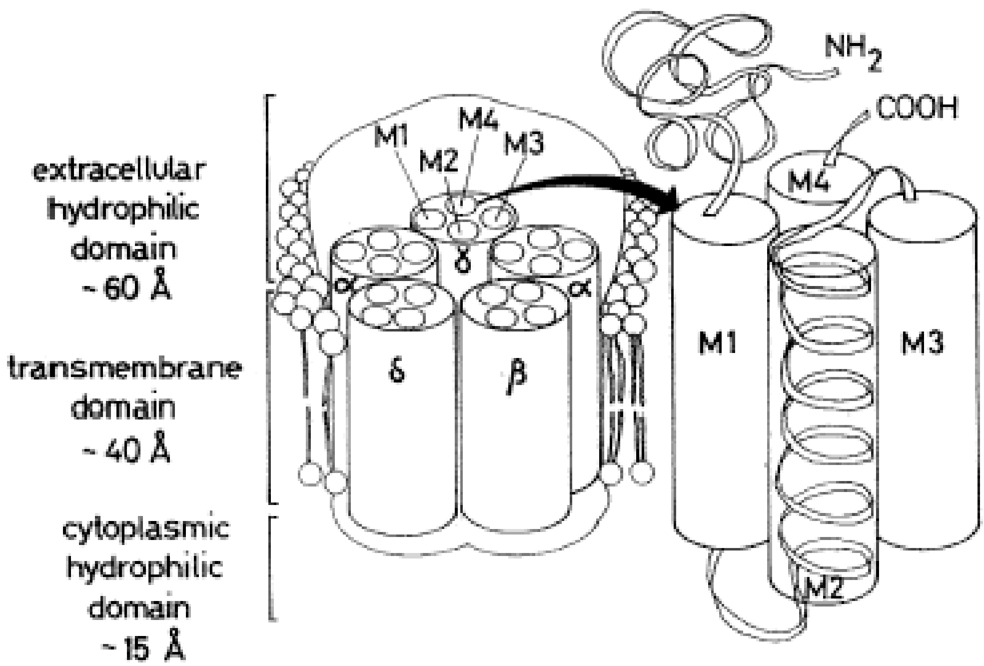


1. Long NH_2-terminal hydrophilic extracellular region (210 A.A., 60 Å)
2. Four highly hydrophobic domains (**M1**, **M2**, **M3** and **M4**)
3. Major hydrophilic segment facing the cytoplasm in which the **M4** domain orientates the CO_2H-terminal towards the synaptic side of the membrane

Arias, H. R. *Neurochem. Int.* **2000**, *36*, 595

Example of Ionotropic Receptor: Nicotinic Acetylcholine Receptor (AChR)

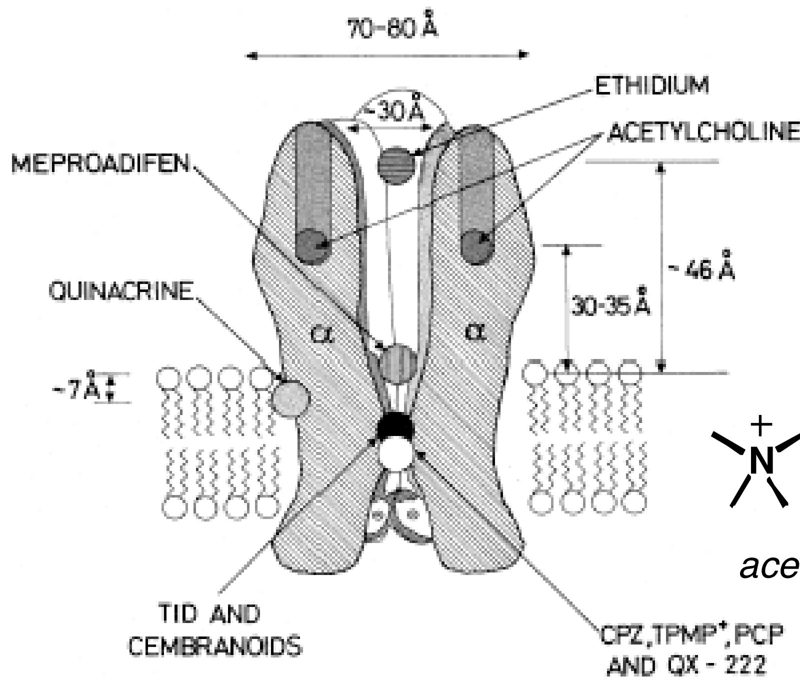
Overall structure of the muscle-type AChR

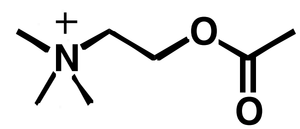


Arias, H. R. *Brain Res. Rev.* **1997**, *25*, 133

Example of Ionotropic Receptor: Nicotinic Acetylcholine Receptor (AChR)

Transverse schematic representation of the muscle-type AChR showing the most probable localisation of both acetylcholine and other ligands

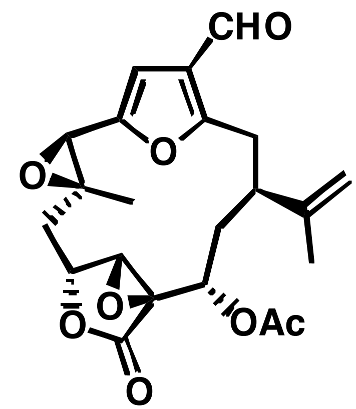




acetylcholine

Arias, H. R. *Brain Res. Rev.* **1997**, *25*, 133

Presentation Outline



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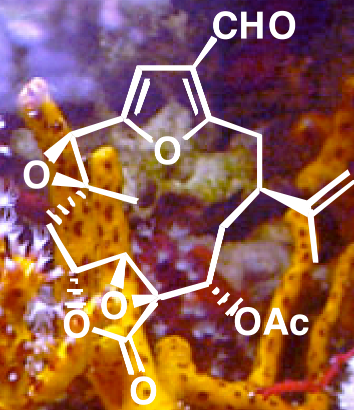
Lophotoxin



White needles
Mp 164–166 °C
$[\alpha]_D^{27}$ +14.2° (*c* = 1.7, $CHCl_3$)

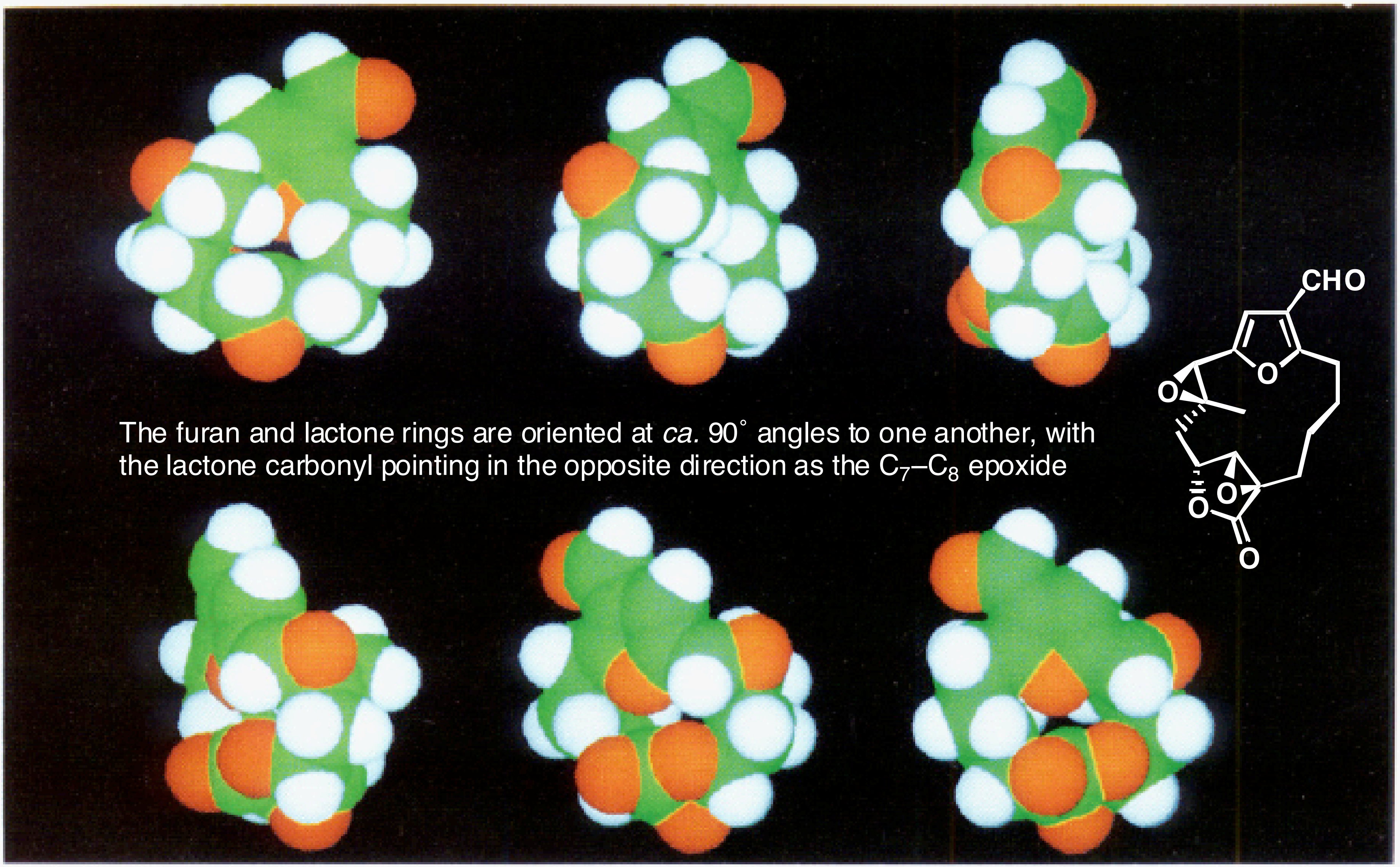
- **First isolated[1] from Pacific Sea whips of the genus *Lophogorgia***
  - found mainly in tropical and subtropical waters (from Panama Bay northward to Point Conception, California)
  - relatively abundant (0.2% dry weight)
  - structure determined by spectral and chemical methods
- **Produced in relatively large quantities by various species of gorgonian corals**
  - 758 g of freeze dried *Lophogorgia violacea* affords 163 mg (0.09%)

[1] Fenical, W.; Okuda, R. K.; Bandurraga, M. M.; Culver, P.; Jacobs, R. S. *Science* **1981**, *212*, 1512

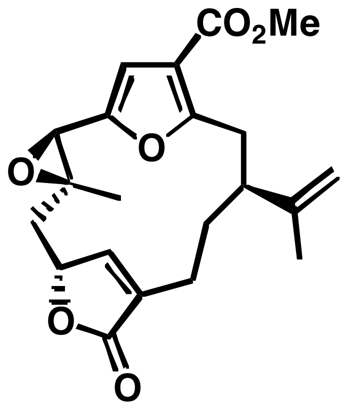
Structural Features

- **Uncharged cyclic diterpene**
- **14-membered macrocycle incorporating a 2,3,5-trisubstituted furan, an epoxidized butenolide ring and a *trans*-trisubstituted epoxide**
- **5 stereogenic centers (2 epoxides, 3 chiral centers)**

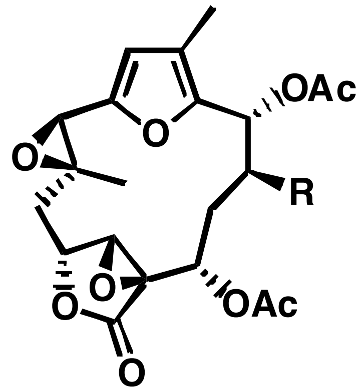
Lophotoxin


The furan and lactone rings are oriented at *ca.* 90˚ angles to one another, with
the lactone carbonyl pointing in the opposite direction as the C_7–C_8 epoxide
CHO
O
O
O
O
O

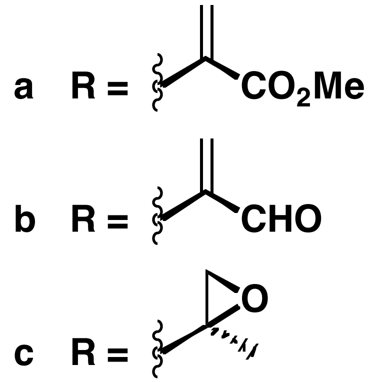
Other Members of the Furanocembranolides

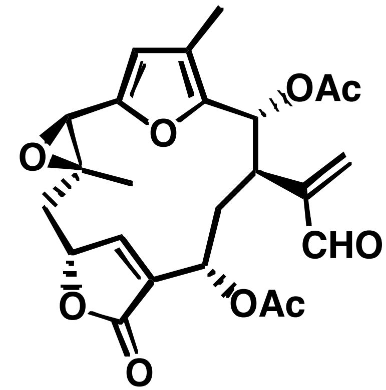


Pukalide[a]

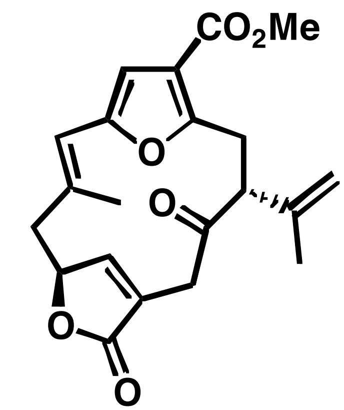


Bipinnatin[b]

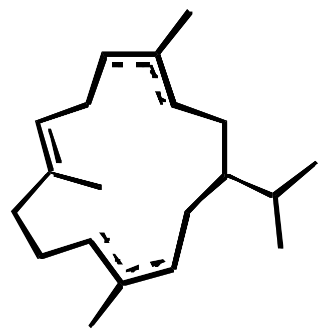




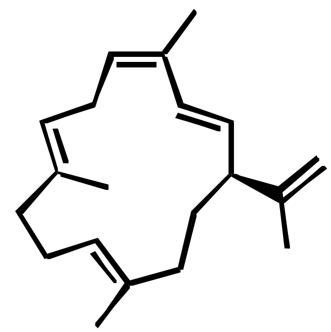
Bipinnatin d[b]



Acerosolide[c]



Cembranoid skeleton



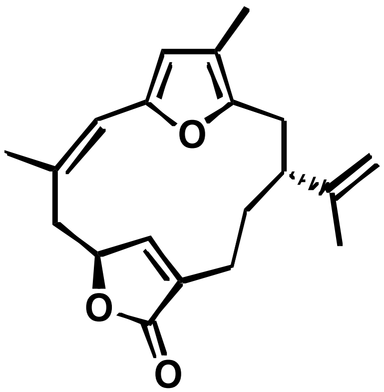
Cembrene

[a] Missakian, M. G.; Burreson, B. J.; Scheuer, P. J. *Tetrahedron* **1975**, *31*, 2513

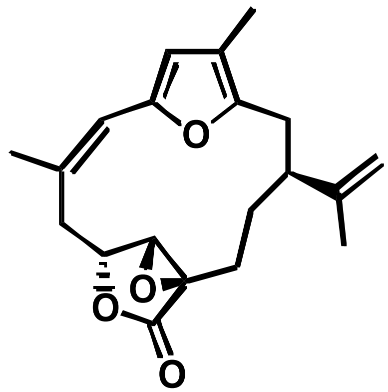
[b] Wright, A. E.; Burres, N. S.; Schulte, G. K. *Tetrahedron Lett.* **1989**, *30*, 3491

[c] Chan, W. R.; Tinto, W. F.; Laydoo, R. S.; Manchaud, P. S.; Reynolds, W. F.; McLean, S. *J. Org. Chem.* **1991**, *56*, 1773

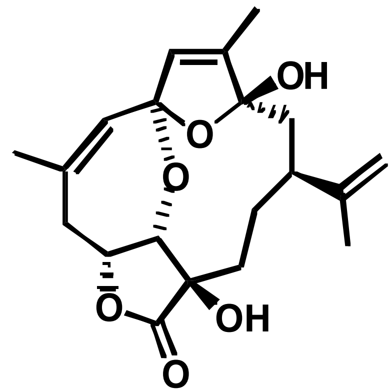
Other Members of the Furanocembranolides



Rubifolide[d]



Coralloidolide A[e]



Coralloidolide B[e]

Total syntheses of Furanocembranes

Bis-deoxylophotoxin, see; Cases, M.; de Turiso, F. G.-L.; Pattenden, G. *Synlett* **2001**, 1869

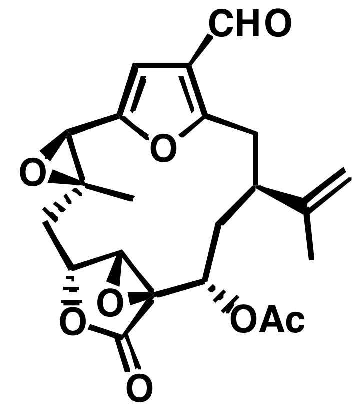
Deoxypukalide, see; Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037

Rubifolide (enantiomer), see; Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313

Acerosolide (racemic), see; Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165

[d] Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332
[e] D'ambrosio, M.; Fabbri, D.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 63

Bioactivity of Lophotoxin



☛ **Causes neuromuscular paralysis by inhibition of nicotinic acetylcholine receptors**

Causes paralysis and asphyxiation (LD_{50} in mice is 8.0 μg/g)

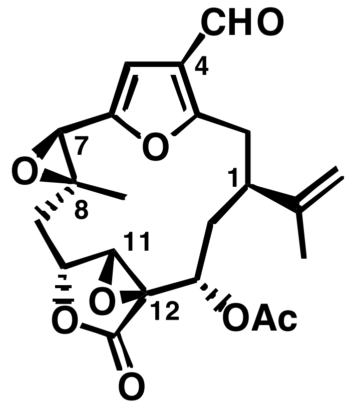
Lophotoxin acts as a competitive antagonist, by reacting covalently with the Tyr^{190} residue (used as a probe to study the role of Tyr^{190} in binding acetylcholine)

☛ **Also inhibits neuronal and peripheral nicotinic acetylcholine receptors**

☛ **Lophotoxin and other furanocembranolides are responsible for the chemical defense displayed by the brazilian octocoral *Lophogorgia violacea* when submitted to feeding experiments to predatory fishes**

Epifanio, R de A,; Maia, L. F.; Fenical, W. *J. Braz. Chem. Soc.* **2000**, *11*, 584

Structure/Activity Studies of the Lophotoxin Family



- Substituents at C_1, C_2 and C_4 are not essential to retain activity
- Epoxide at C_{11}–C_{12} is not critical either (however, the involvement of C_{11} in the irreversible binding has not been ruled out)
- Epoxide at C_7–C_8 is very important and is likely to be involved in the covalent reaction with the receptor
- C_{13} acetate is *not absolutely required* (12-fold decrease in activity for the hydrolized derivative)
- Reduction of the lactone carbonyl to a cyclic hemiacetal produces a dramatic decrease in activity, which apparently results from a decrease in affinity for the recognition site

Abramson, S. N.; Trischman, J. A.; Tapiolas, D. M.; Harold, E. E.; Fenical, W.; Taylor, P. *J. Med. Chem.* **1991**, *34*, 1798

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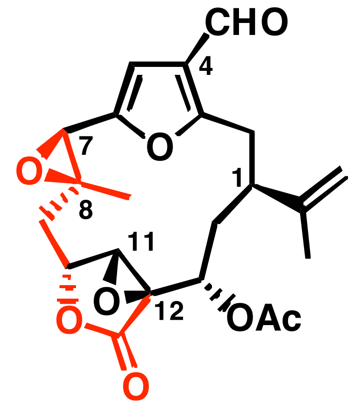

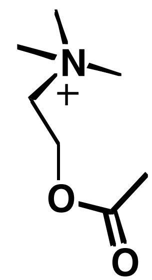

Acetylcholine

- Substituents at C_1, C_2 and C_4 are not essential to retain activity
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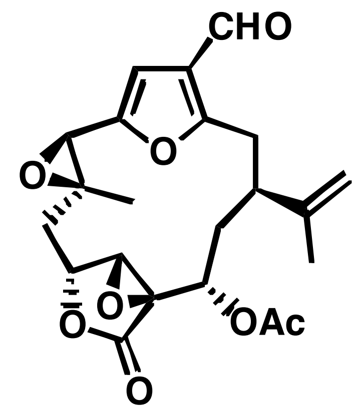

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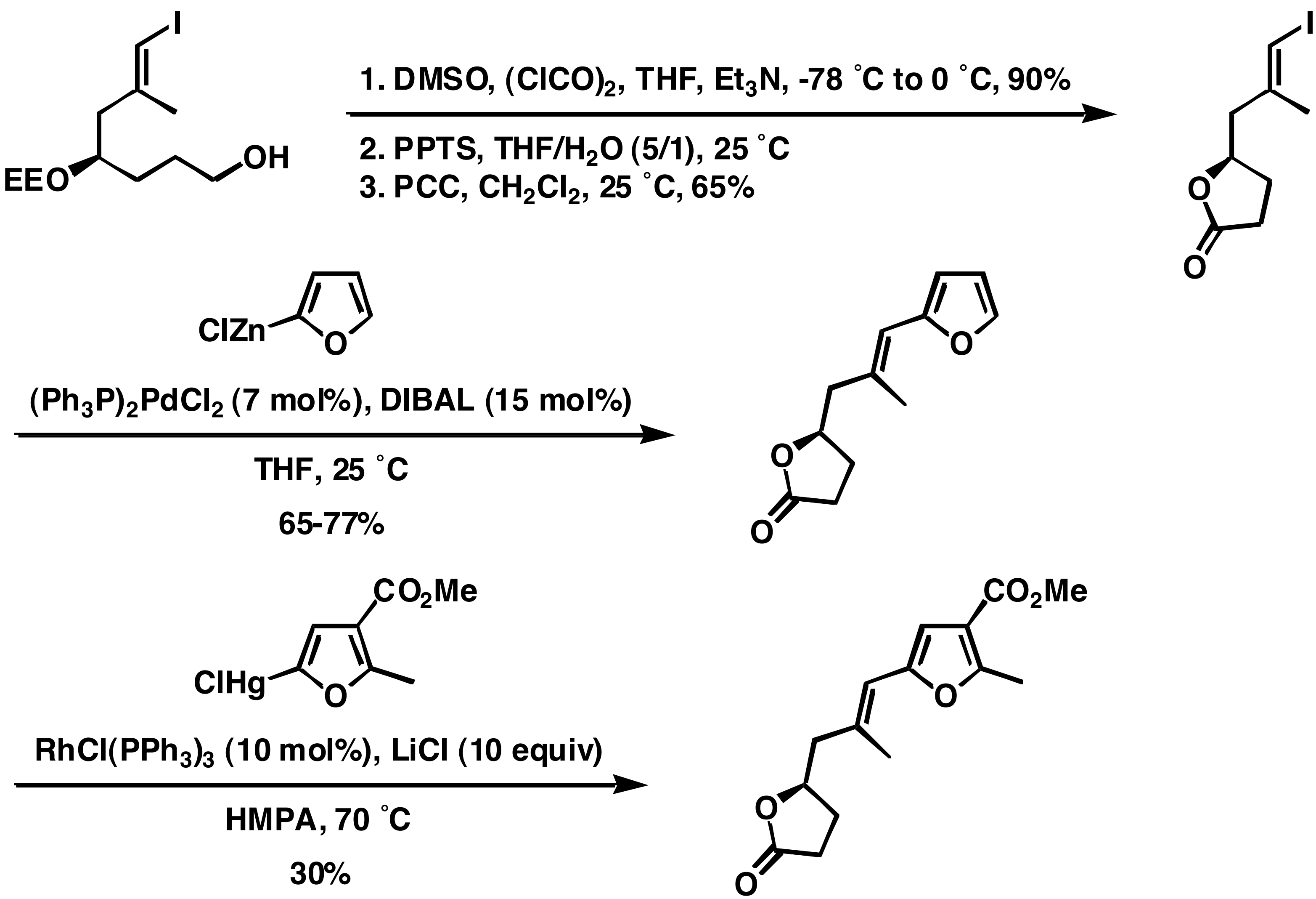
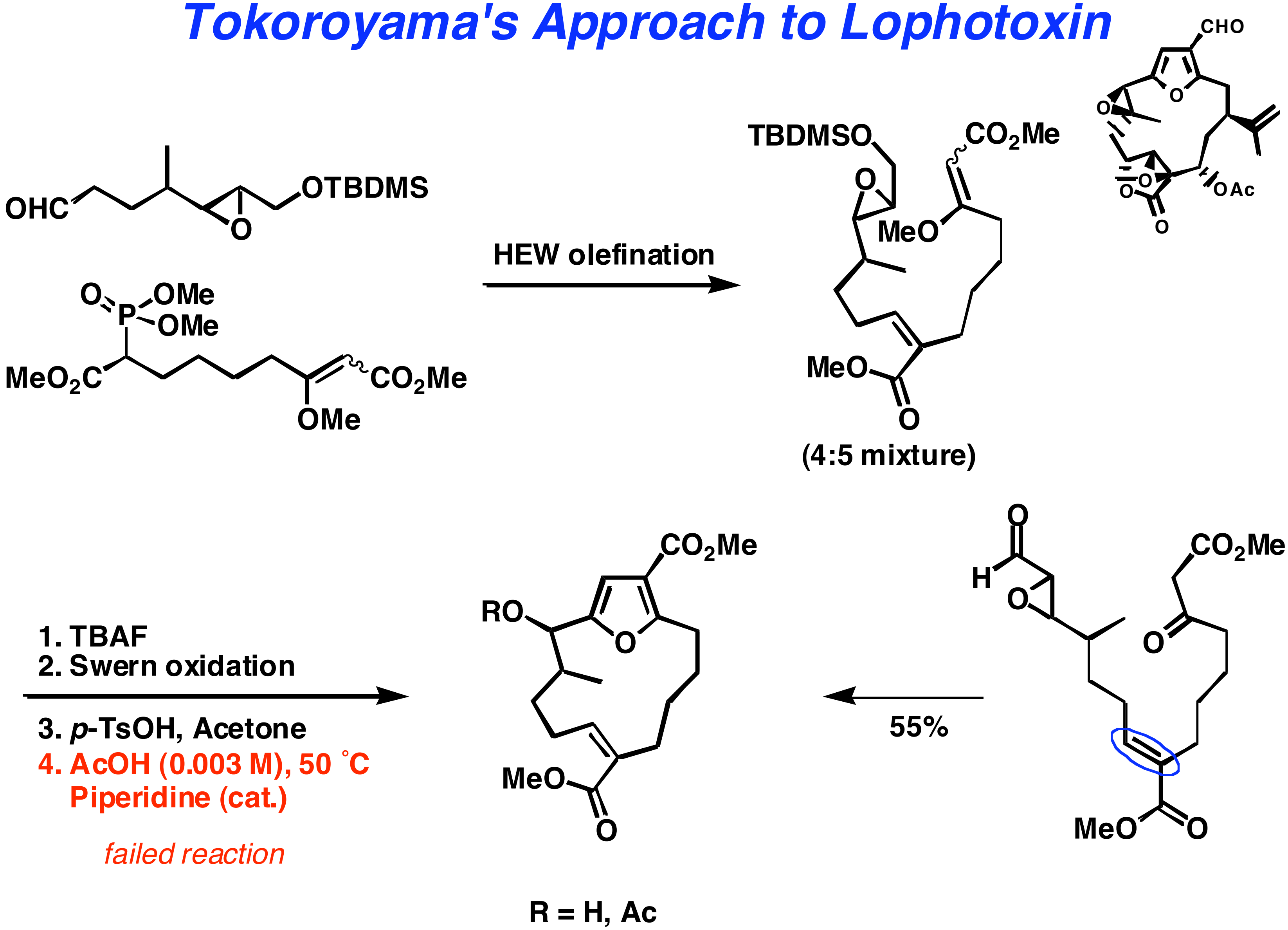
Tius' Approach to Lophotoxin



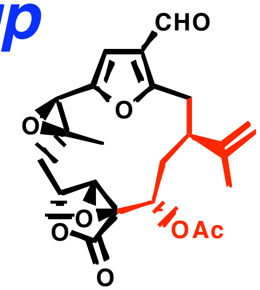
Tius, M. A,; Trehan, S. *J. Org. Chem.* **1986**, *51*, 767

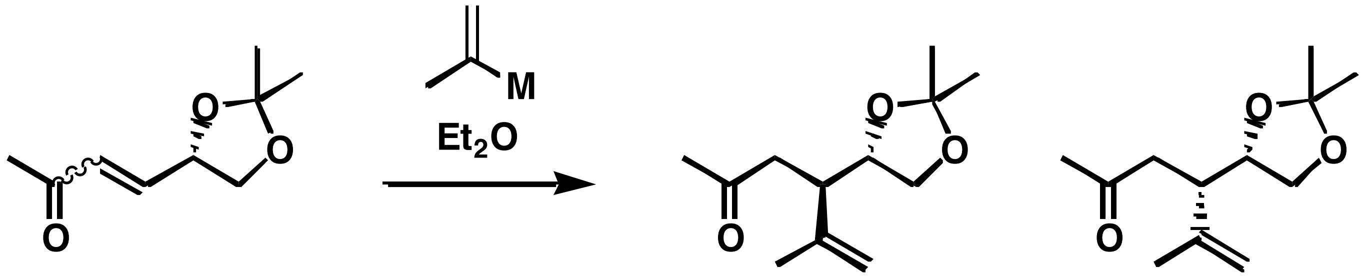
Tokoroyama's Approach to Lophotoxin



Kondo, A.; Ochi, T.; Ilo, H.; Tokoroyama, T.; Siro, M. *Chem. Lett.* **1987**, 1491

Incorporation of the Isopropenyl Group by Conjugate Addition





anti *syn*

Entry	Enone	T (˚C)		Additive	*anti:syn*
1	*Z*	-100	RCu	none	8:1
2	*Z*	-78	RCu	TMSCl	6:1
3	*Z*	-78	RCu	$BF_3 \cdot Et_2O$	6:1
4	*Z*	-100	R_2CuLi	none	4:1
5	*Z*	-100	$R_2CuCNLi_2$	none	7:1
6	*E*	-100	RCu	none	5:1
7	*E*	-100	R_2CuLi	none	3:1

Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525

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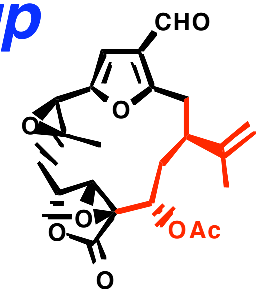
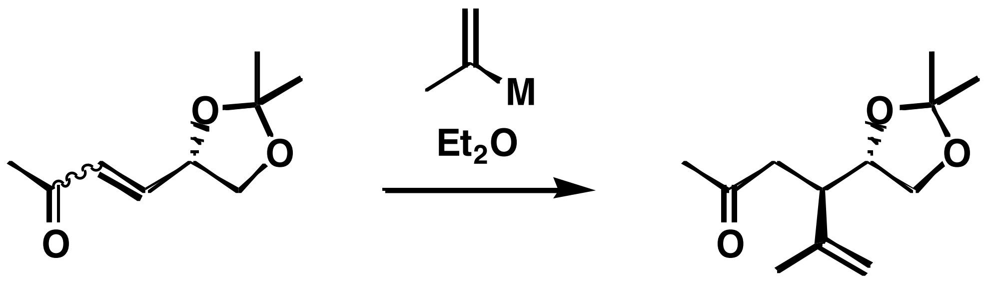
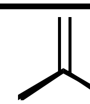
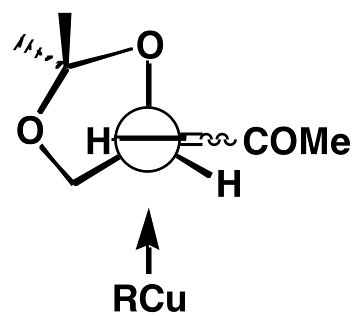




anti *syn*

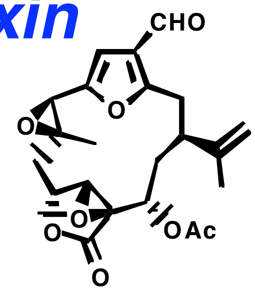
Entry	Enone (E:Z)	T (˚C)	 M	Yield (%)	*anti:syn*
1	6:1	-78	RCu	79	7:1
2	7:2	-100	RLi	60	1:36

Felkin-Anh transition state

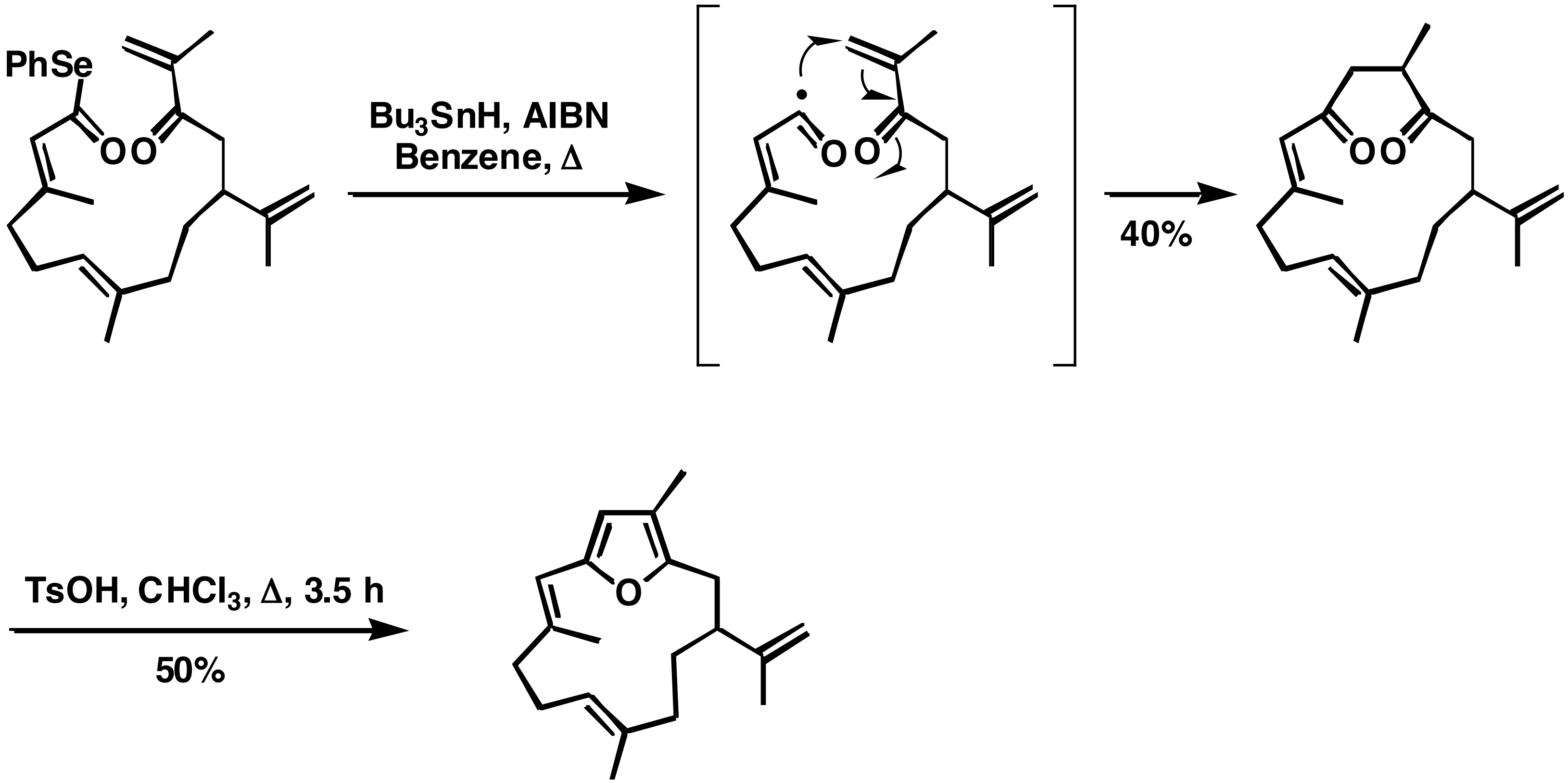


Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525

Pattenden's First Approach to Lophotoxin

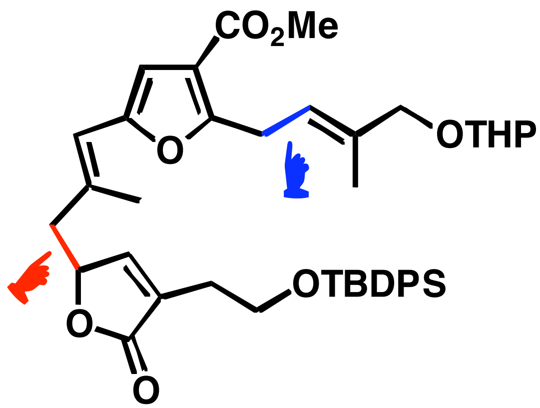


Acyl Radical Macrocyclization Strategy

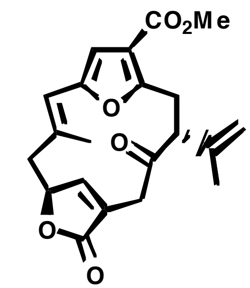


Astley, M. P.; Pattenden, G. *Synthesis* **1992**, 101

Paquette's Approach to Acerosolide



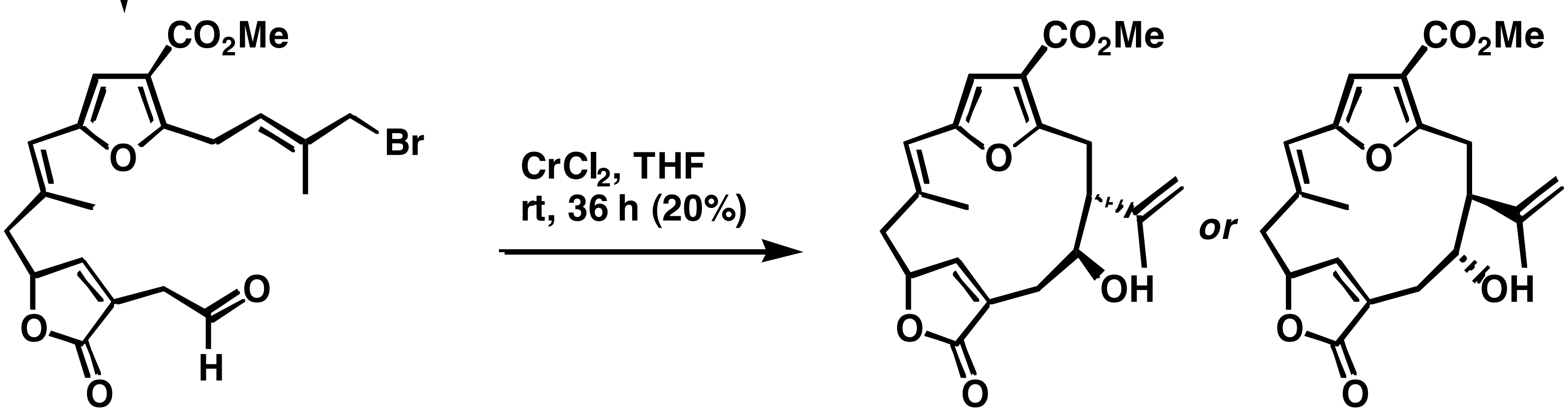
Allylstannane addition to aldehyde ($SnCl_4$)
sp^3–sp^2 Stille coupling
racemic synthesis



1. $Ph_2PCH_2CH_2PPh_2 \cdot Br_2$
CH_2Cl_2, 0 °C (64%)
2. HF, ACN/H_2O (68%)
3. PDC, MS, CH_2Cl_2, 0 °C (46%)

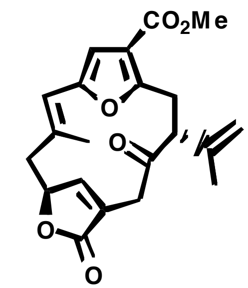
Oxidation with PDC in DMF affords Acerosolide

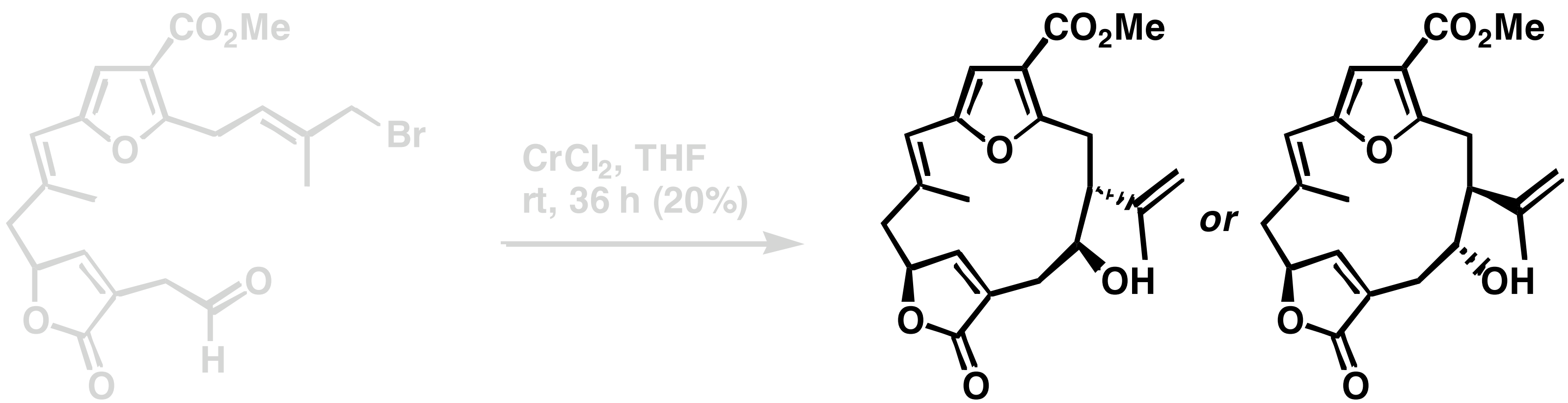
Possibility of epimerization during the oxidation step

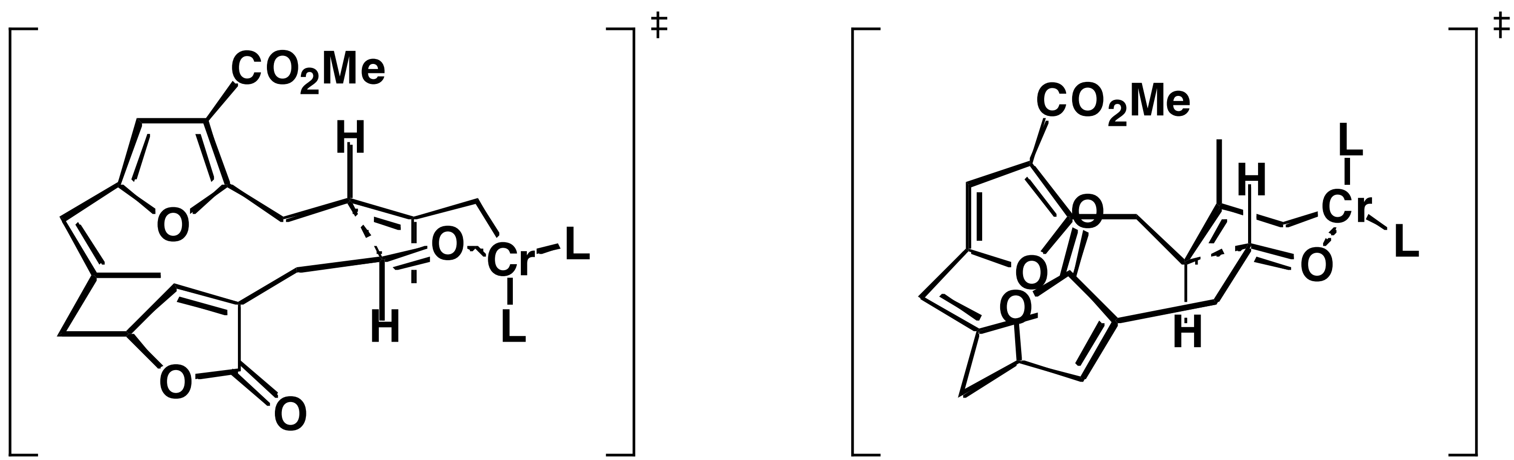


Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165

Paquette's Approach to Acerosolide

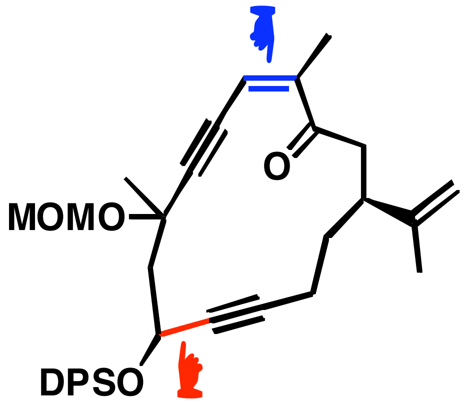




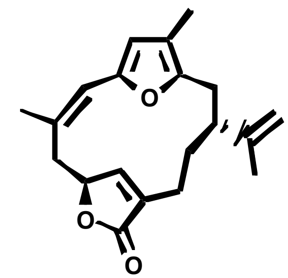


Paquette, L. A.; Astles, P. C. *J. Org. Chem.* **1993**, *58*, 165

Marshall's Approach to Rubifolide

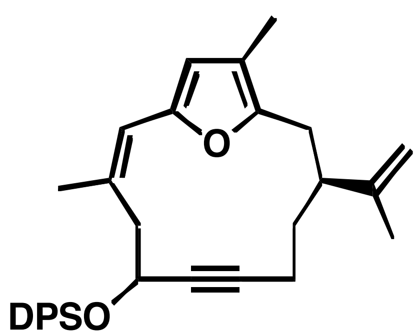


Lithium acetylide addition
HEW olefination



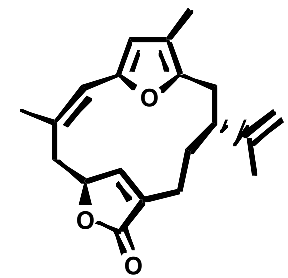
1. DIBALH
2. KO*t*-Bu, *t*-BuOH
THF, 18-C-6

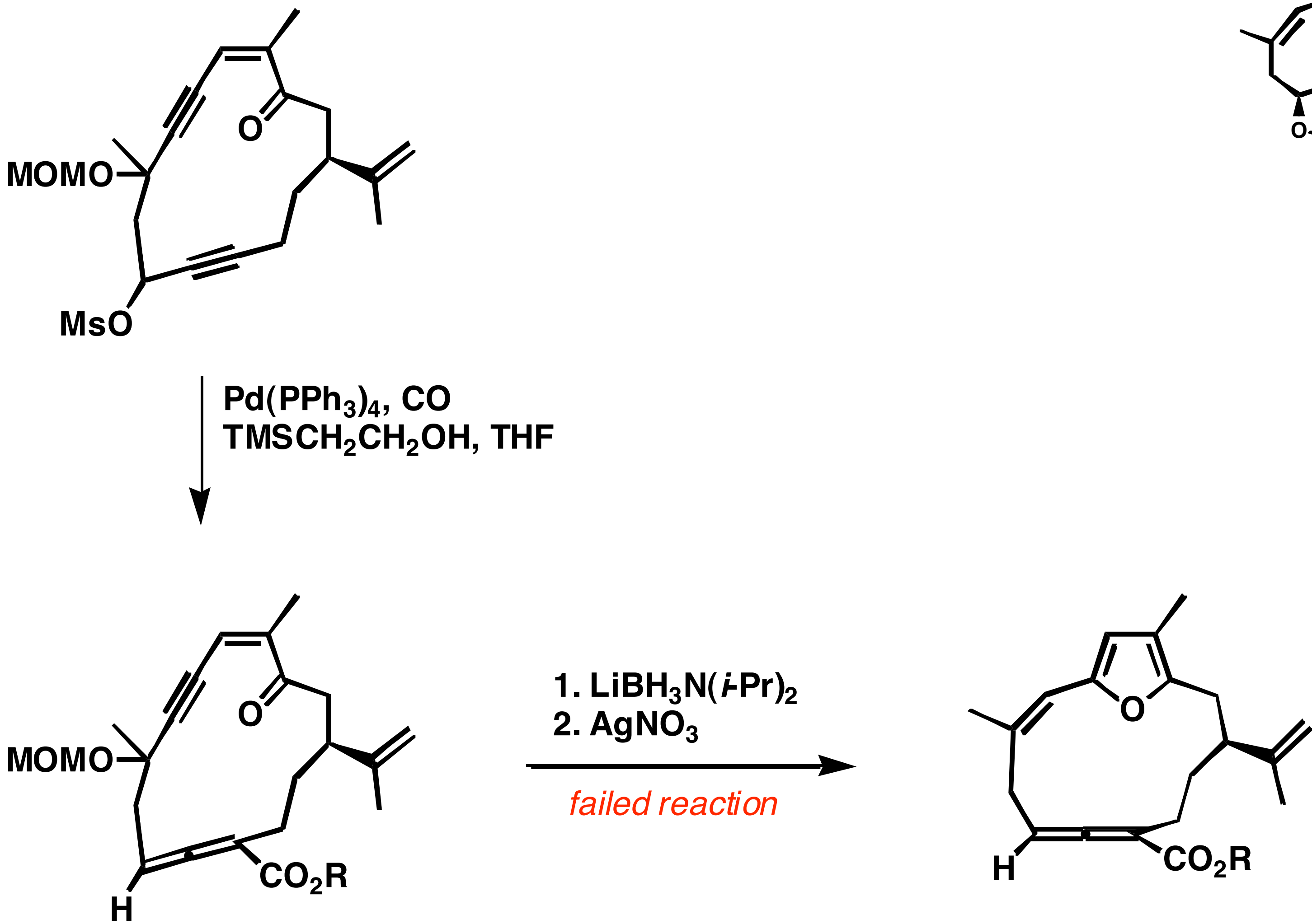
failed reaction



Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313

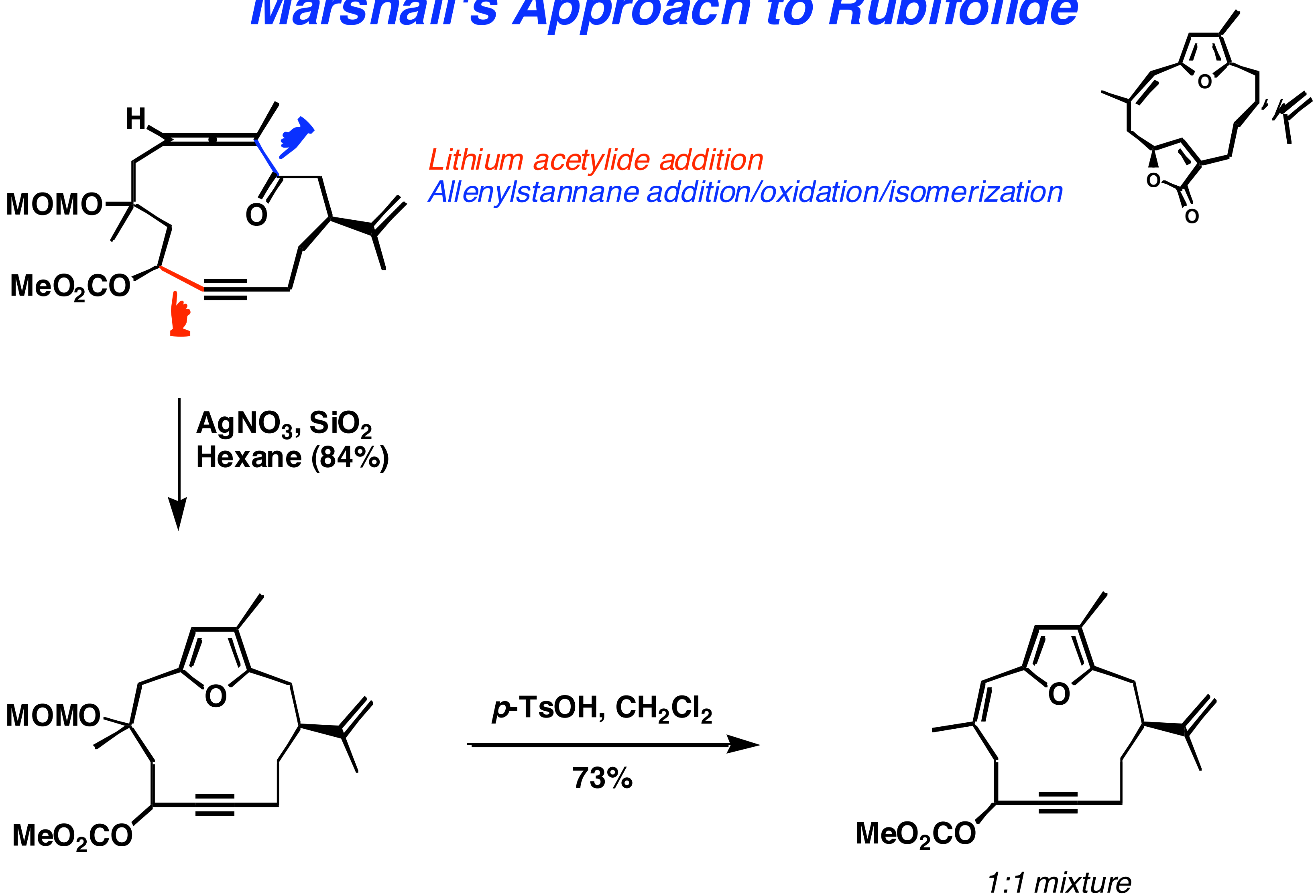
Marshall's Approach to Rubifolide





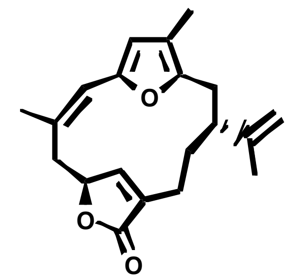
Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313

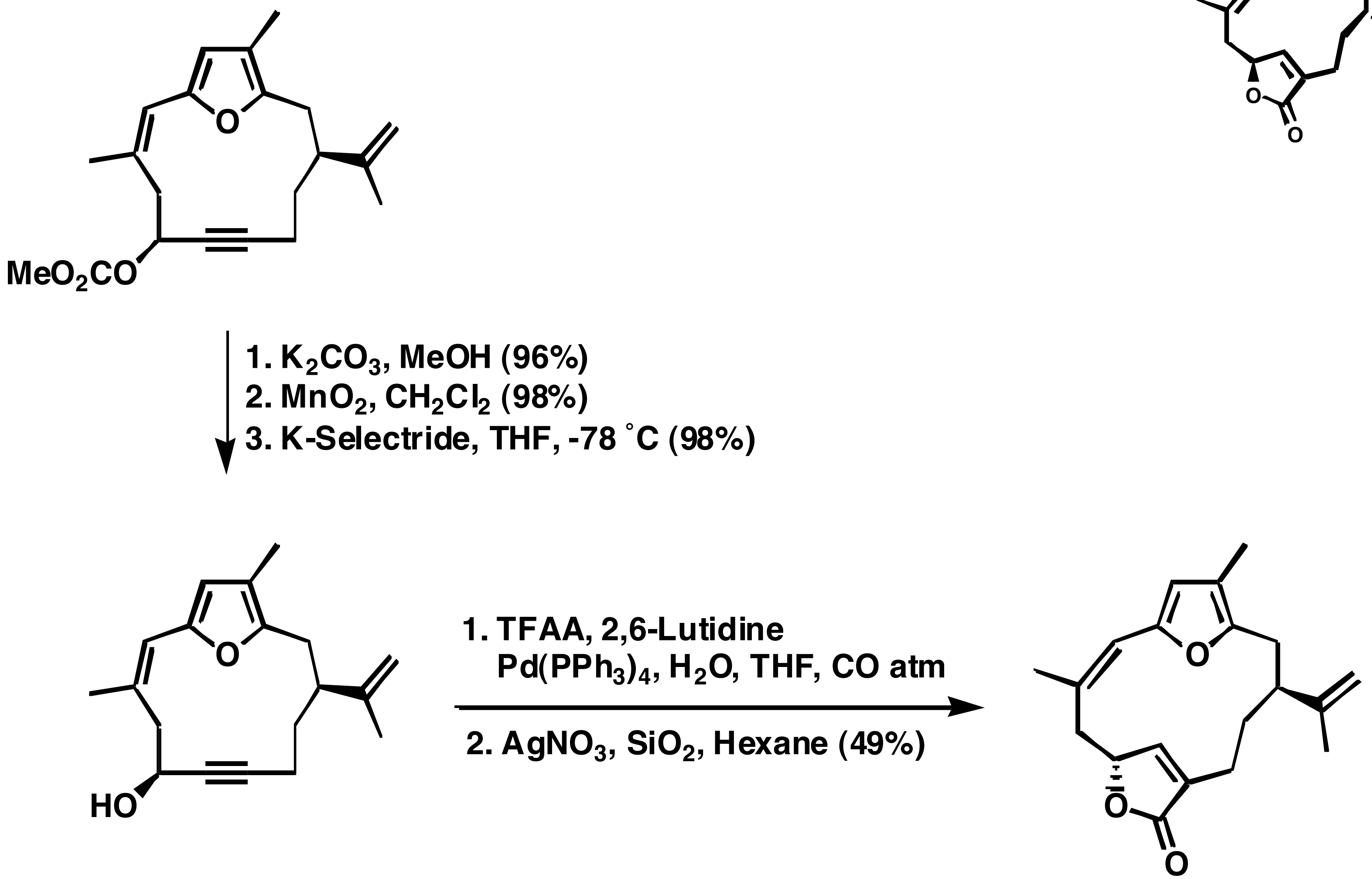
Marshall's Approach to Rubifolide



Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313

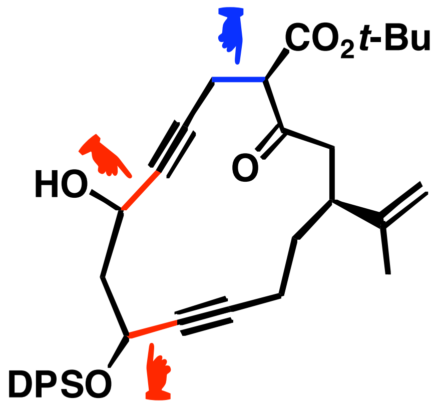
Marshall's Approach to Rubifolide

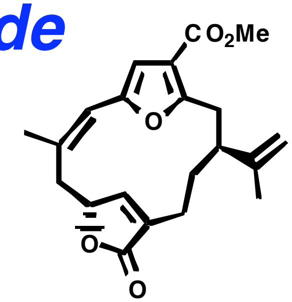




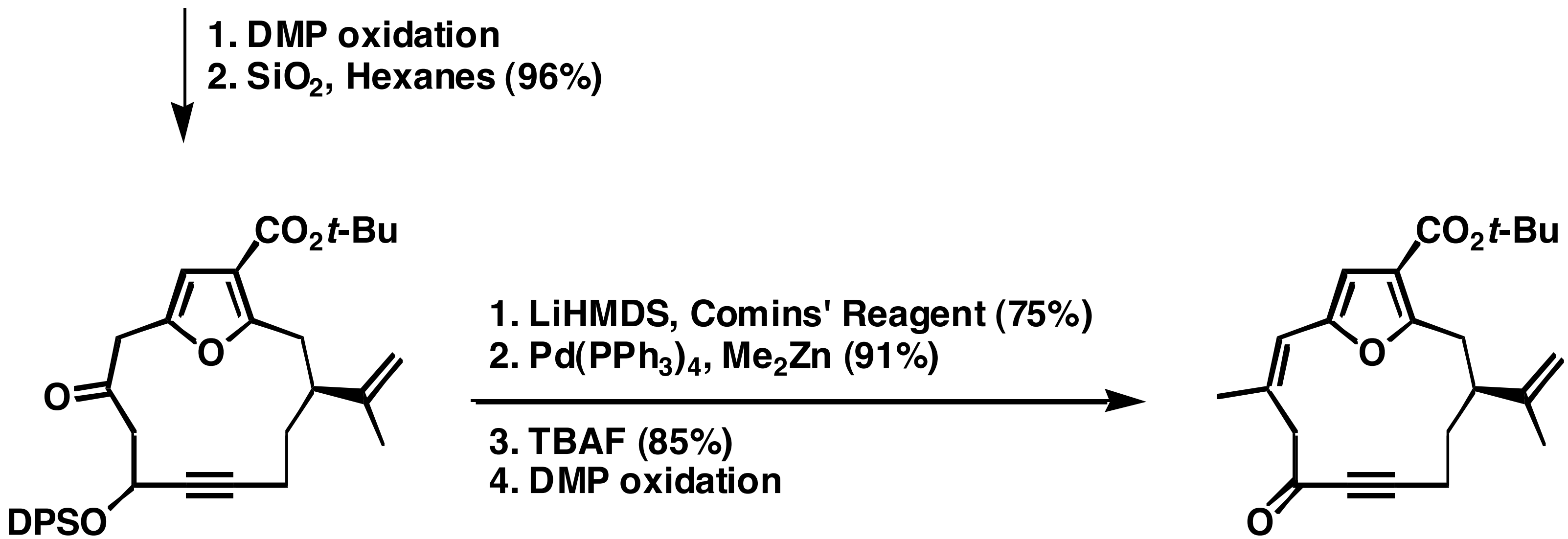
Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313

Marshall's Approach to Deoxypukalide



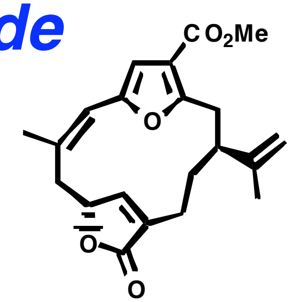


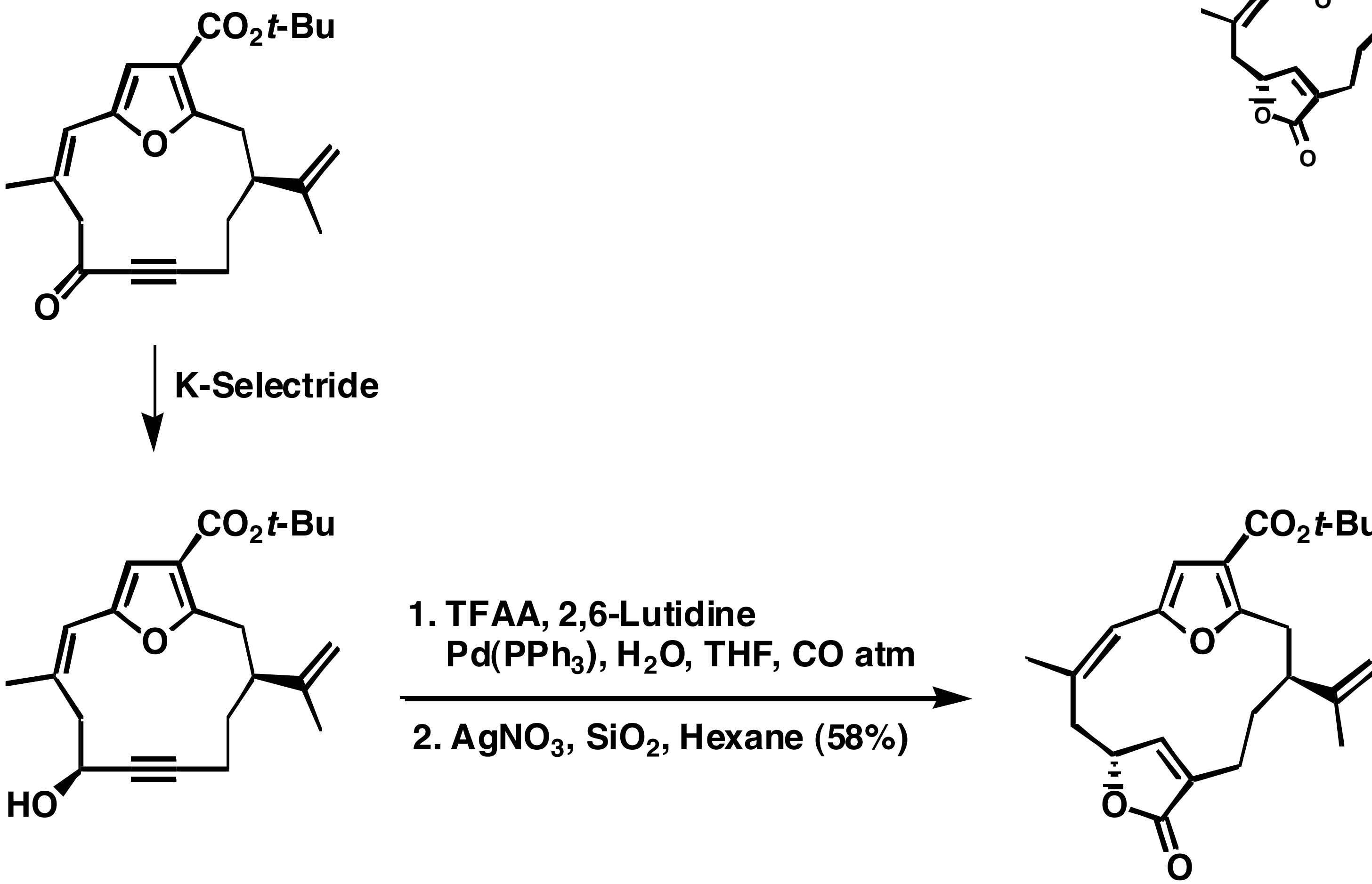
Lithium acetylide addition
β-keto ester alkylation
mixture of 8 diastereoisomers



Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037

Marshall's Approach to Deoxypukalide

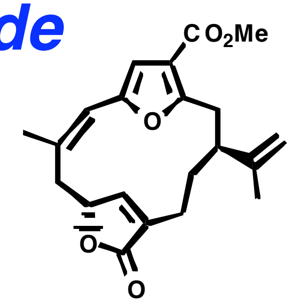


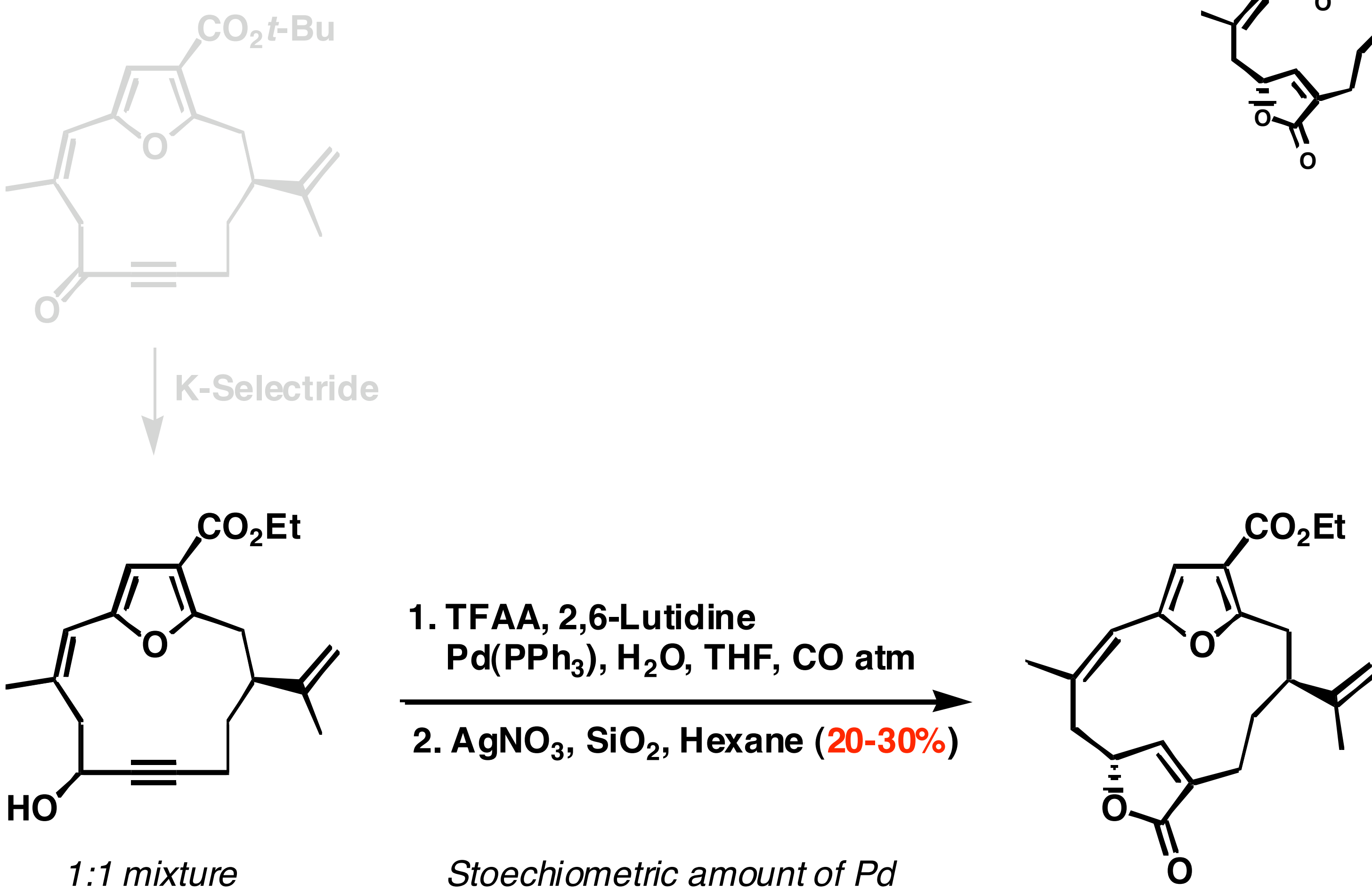


Thermolysis (210 ˚C) and treatment with $TMSCHN_2$ affords Deoxypukalide

Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037

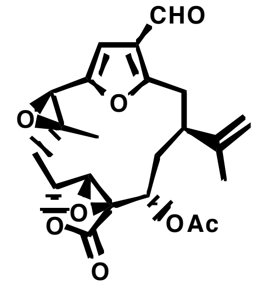
Marshall's Approach to Deoxypukalide

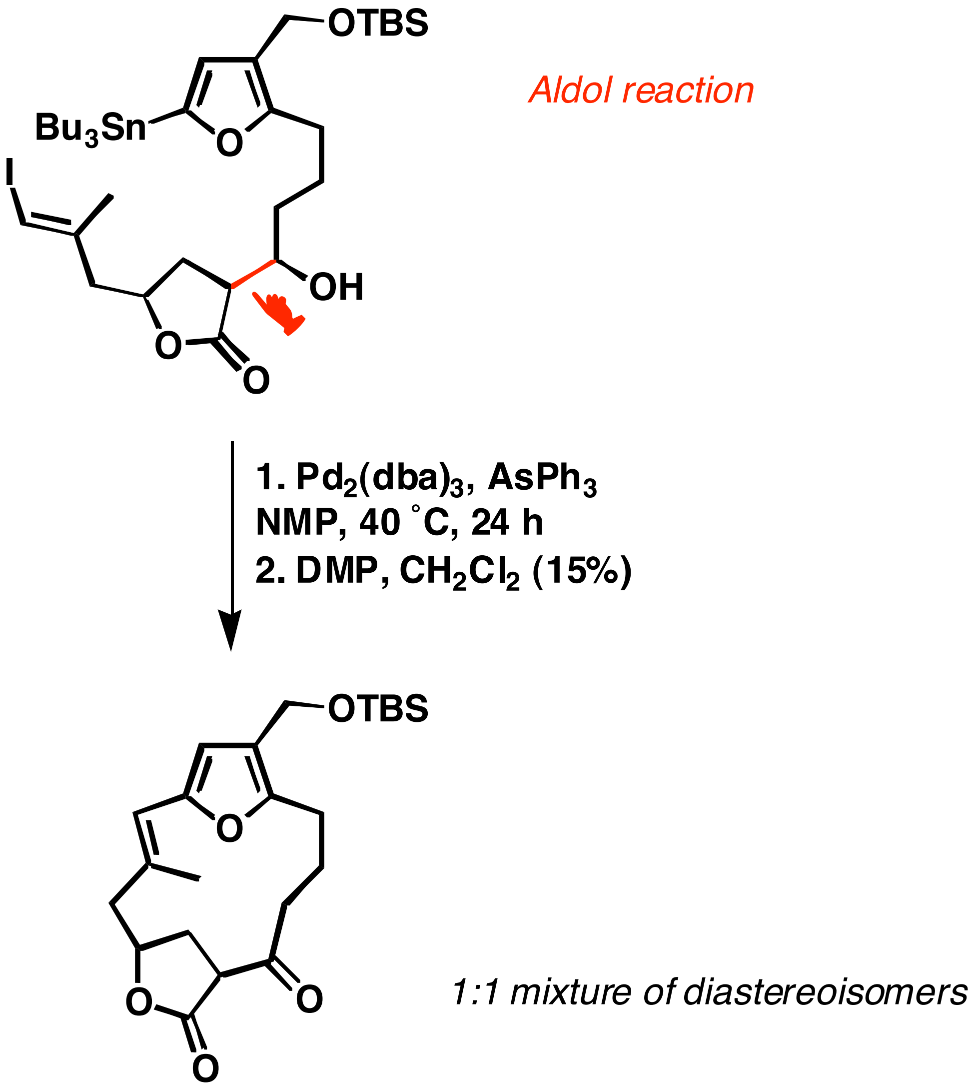




Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037

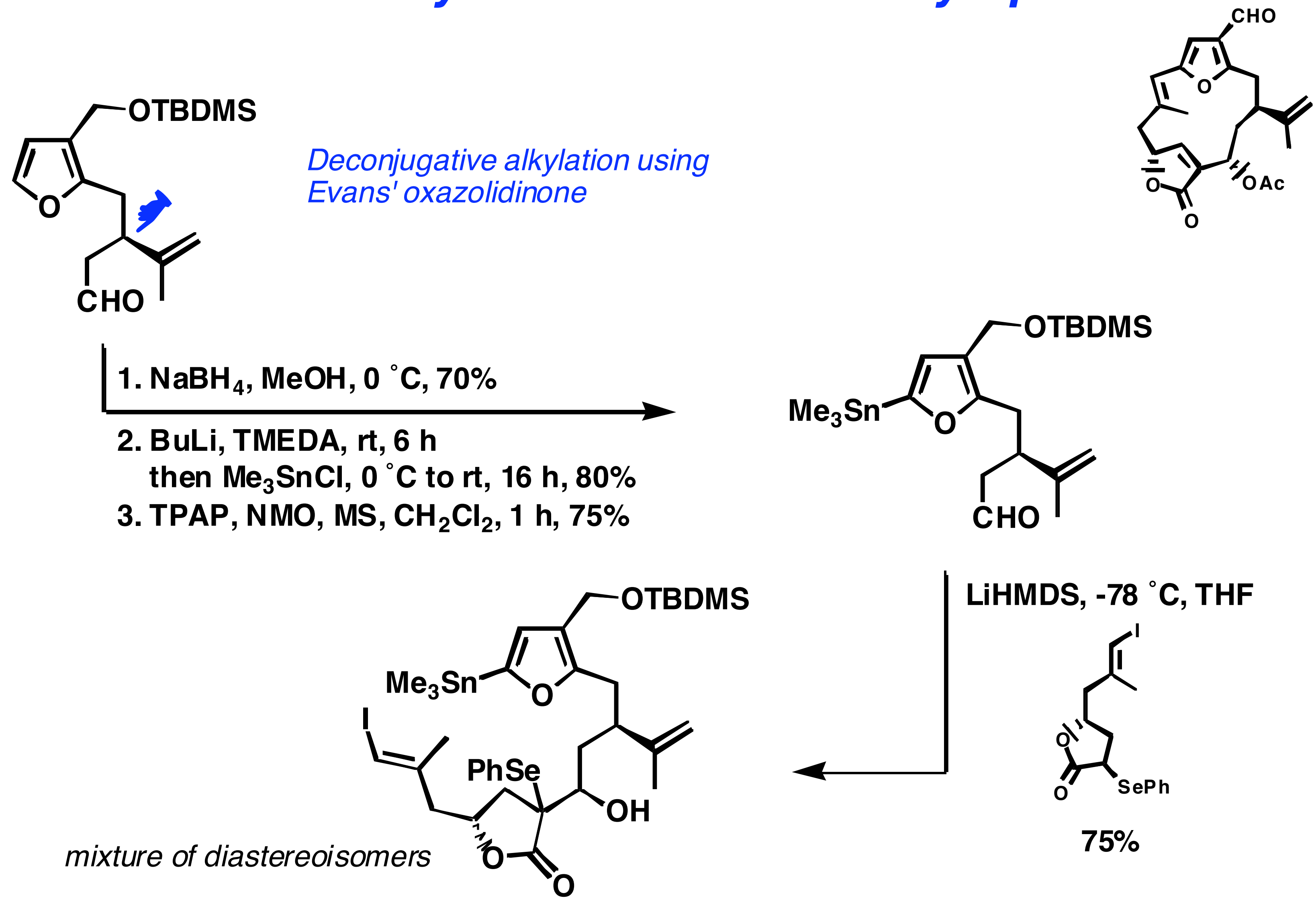
Paterson's Approach to Lophotoxin





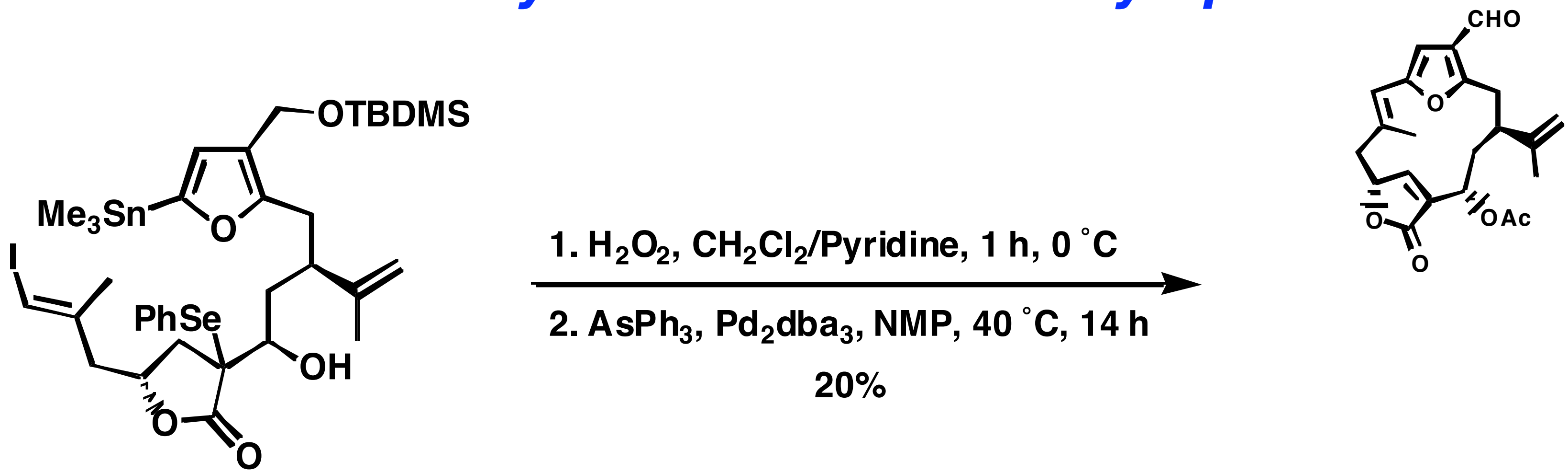
Paterson, I.; Brown, R. E.; Urch, C. J. *Tetrahedron Lett.* **1999**, *40*, 5807

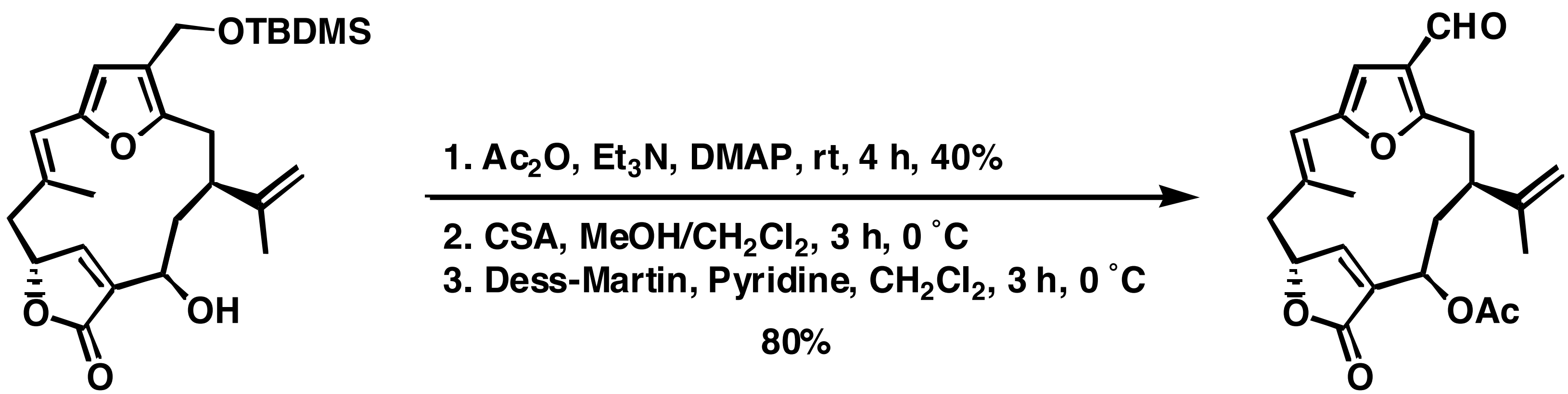
Pattenden's Synthesis of bis-Deoxylophotoxin



Cases, M.; de Turiso, F. G.-L.; Pattenden, G. *Synlett* **2001**, 1869

Pattenden's Synthesis of bis-Deoxylophotoxin

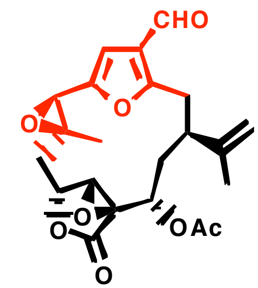




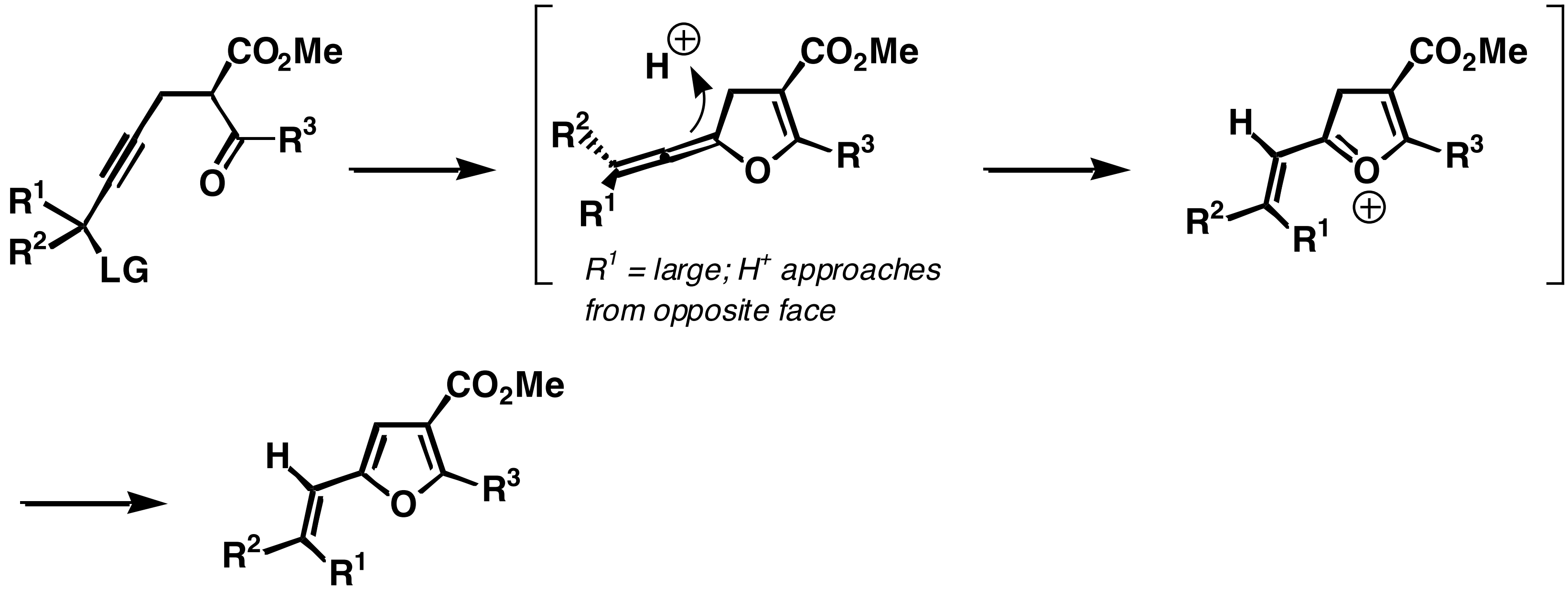
For a short review on the application of the intramolecular Stille reaction in some target natural product syntheses

Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261

Wipf's Approach to Lophotoxin

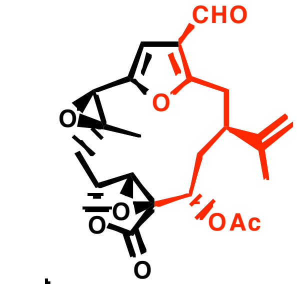


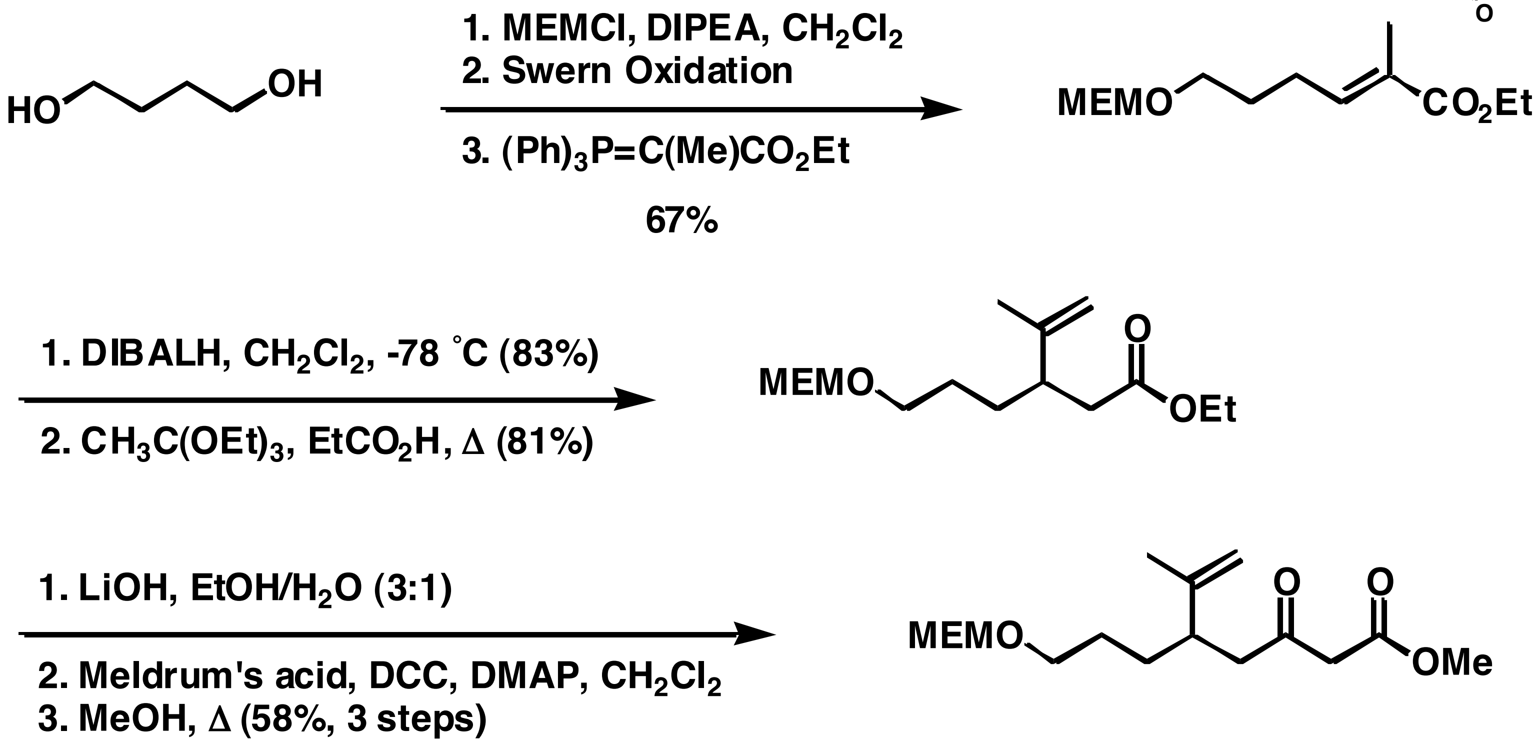
Key step: cyclization of an α-propargyl β-keto ester



Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132

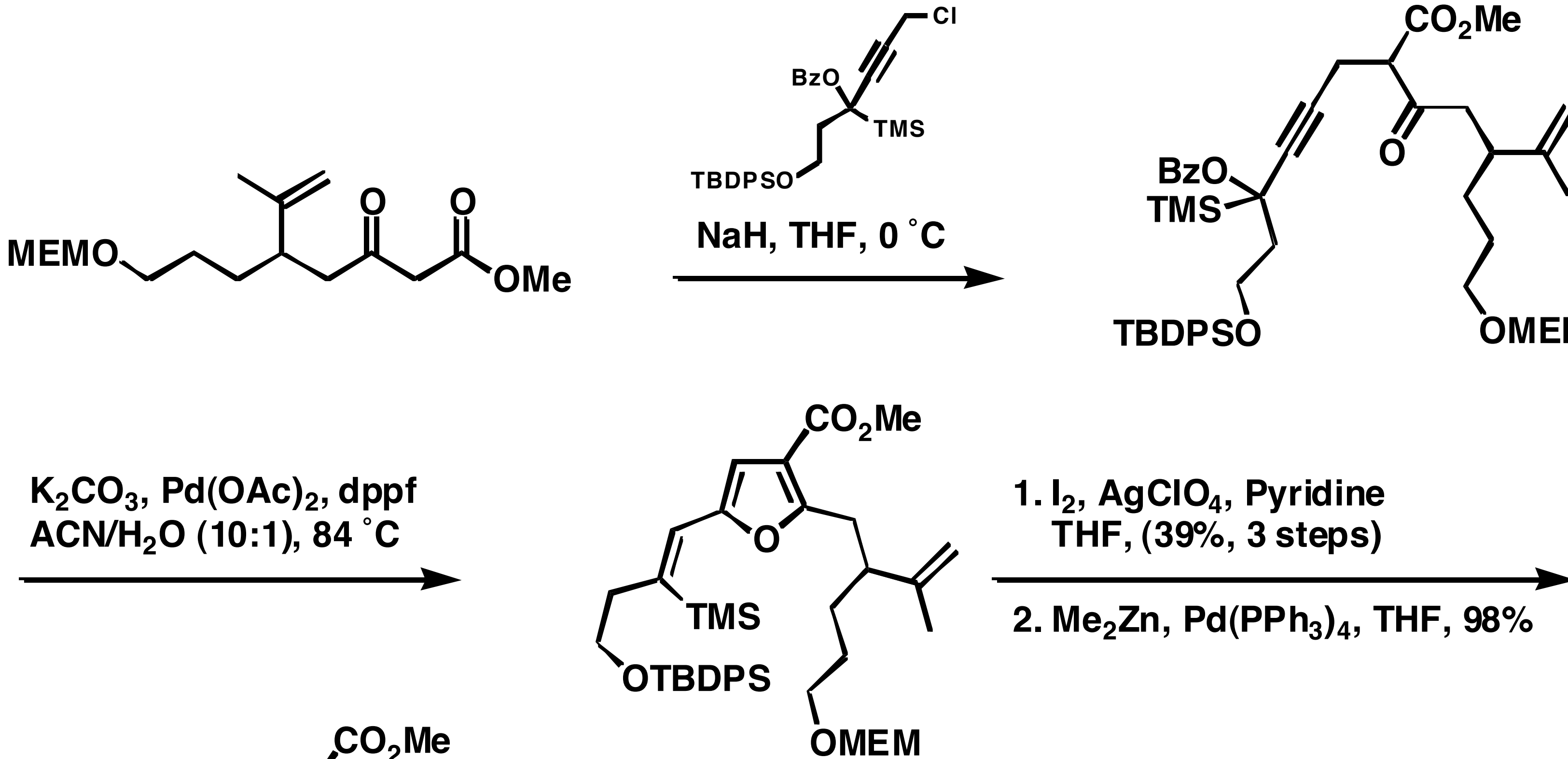
Wipf's Approach to Lophotoxin

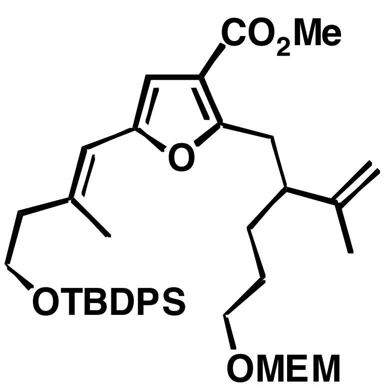




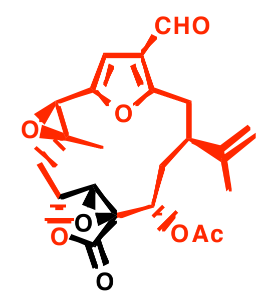
Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787

Wipf's Approach to Lophotoxin



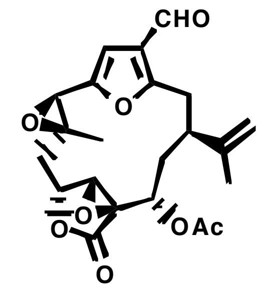


Attach the missing carbon
Incorporate the acetate group
Stereoselective introduction of the isopropenyl



Wipf, P.; Soth, M. J. *Org. Lett.* **2002**, *4*, 1787

Future Work



☛ **Develop a way to introduce the isopropenyl group in a diastereoselective way**

☛ **Find an efficient way to convert the methyl ester to a terminal alkyne**