# *Natural Products with Halogen-Bearing Stereogenic Centers: Natural Origin and Synthesis*

Dr. Jared T. Shaw

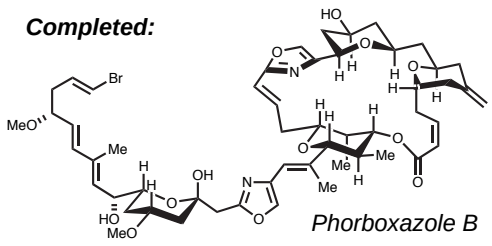
*Evans Group Seminar*
*February 1, 2002*

***Occurrence of Halogenated Natural Products:***
Gribble, G. W., *Progress in the Chemistry of Organic Natural Products*, **1996**, *68*, 1-498. ***2288 references!***
Gribble, G. W., *Acc. Chem. Res.*, **1998**, *31*, 141-152.
***Constituents of* Laurencia:**
Erickson, K. L., *Marine Natural Products*, **1983**, 31-256.
***Fluorinated Natural Products:***
Harper, D. B., O'Hagan, D. O., *Natural Product Reports*, **1994**, *11*, 123-133.
***Haloperoxidases:***
Butler, A., Walker, J. V., *Chem. Rev.*, **1993**, *93*, 1937-1944.
Butler, A., *Coord. Chem. Rev.*, **1999**, *187*, 17-35.
Franssen, M. C. R., *Catalysis Today*, **1995**, *22*, 441-457.
***Synthesis of Halogenated Natural Products:***
Murai, A., *Studies in Natural Products Chemistry*, **1997**, *19*, 411-461.

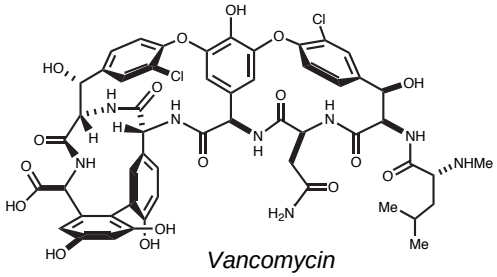
---

## *Halogenated Natural Products Synthesized in the Evans Group*

***Completed:***

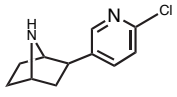


*Phorboxazole B*

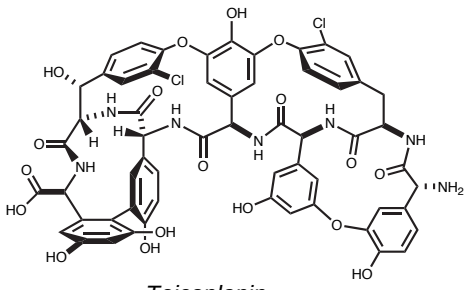


*Vancomycin*

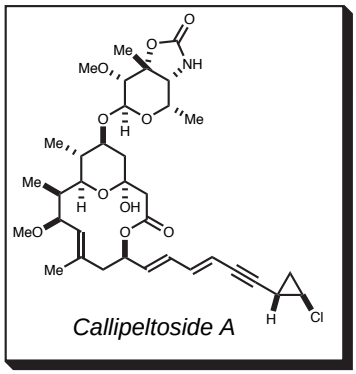
***In Progress:***



*Epibatidine*

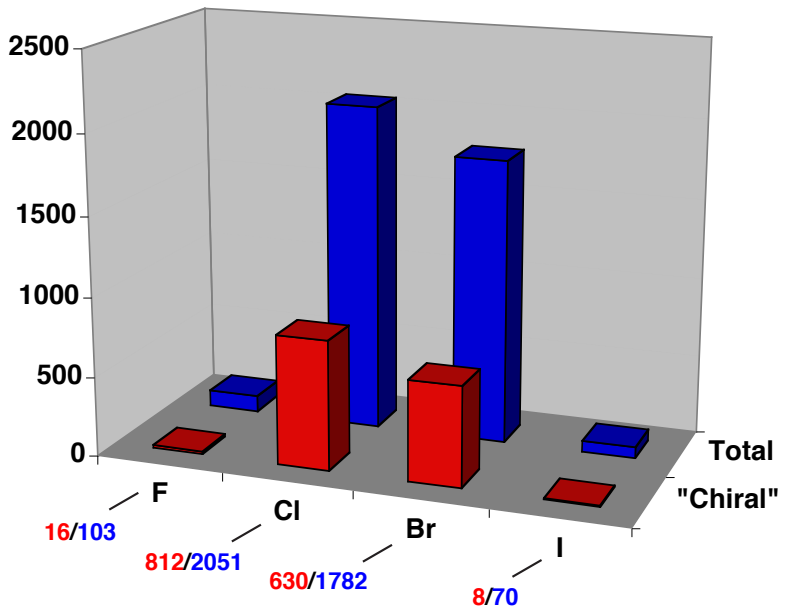


*Teicoplanin*



*Callipeltoside A*

## *Distribution of Halogenated Natural Products*




"**Chiral**" = ***Contains A Halogen-Bearing Stereocenter***

---

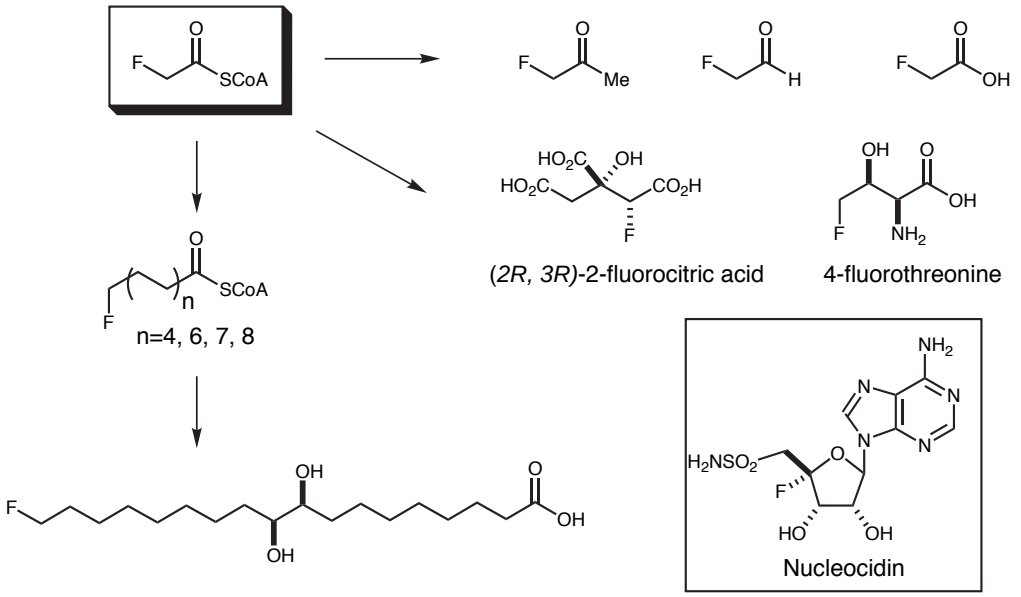
## *Outline*

I. Fluorinated natural products
II. Chlorinated/brominated natural products
  A. biogenesis
  B. Methods of stereoselective chlorination and bromination
    1. $S_N2$ Displacement: "$X^-$"
    2. Electrophilic halogenation: "$X^+$"
    3. Polycyclization
    4. Acyclic stereocontrol employing haloalkenes
    5. The Kharasch reaction
  C. Syntheses
    1. Oppositiol, prepinnaterpene, laurencial, dactylyne
    2. Comparative syntheses of laurencin and related structures
    3. Comparative syntheses of kumausyne and kumausallene
    4. Syntheses aplysiapyranoids and thyrsiferol/venusatriol by electrophilic monocyclization
    5. Selected polycyclzations leading to natural products
    6. Diels-Alder spproaches to plocamium natural products and virantmycin
    7. Callipeltoside sidechain
    8. Halomon
    9. Outlyers: Hapalindole G & Axinellamines

shaw 03/04 2/4/02 1:56 PM

## *The Fluorinated Natural Products*

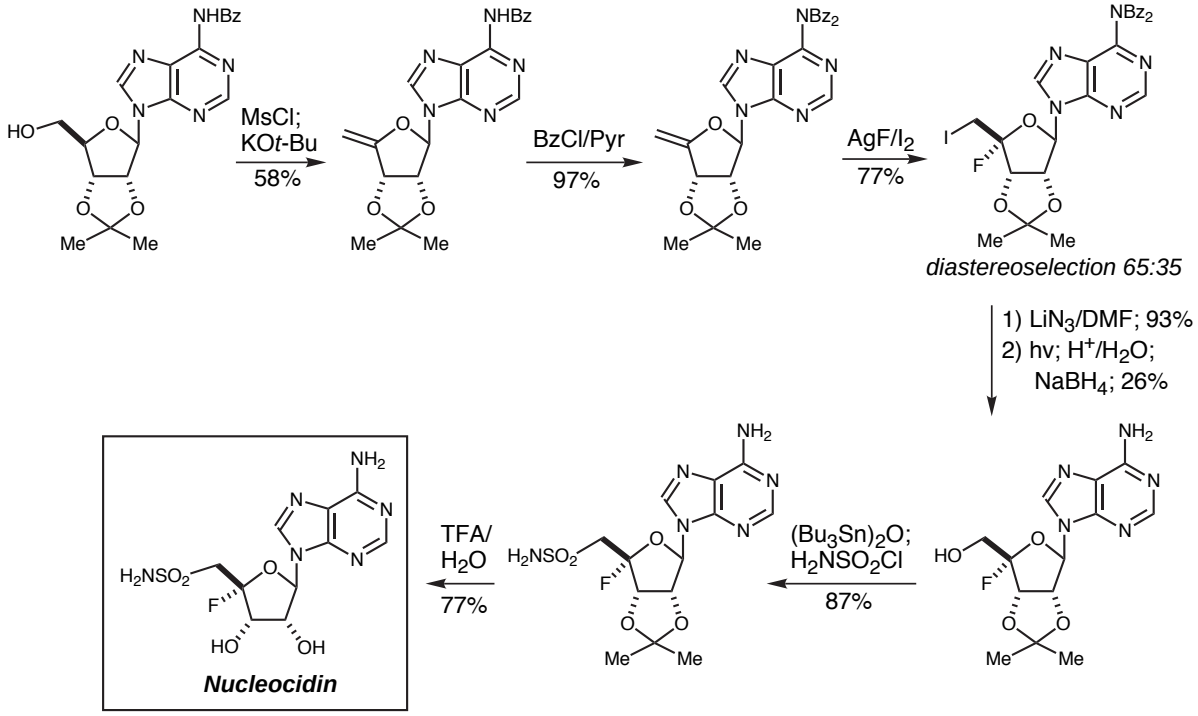
*•Most fluorinated natural products are derived from fluoroacetyl Co-A*




Gribble, 1996

---

## *The Fluorinated Natural Products: Moffatt's Synthesis of Nucleocidin*

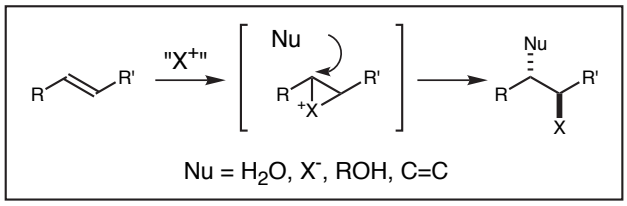



Moffatt, J. G., et al, *J. Am. Chem.Soc.*, **1976**, *98*, 3346-3357.

## *The Biogenic Origin of Halogenated Natural Products*

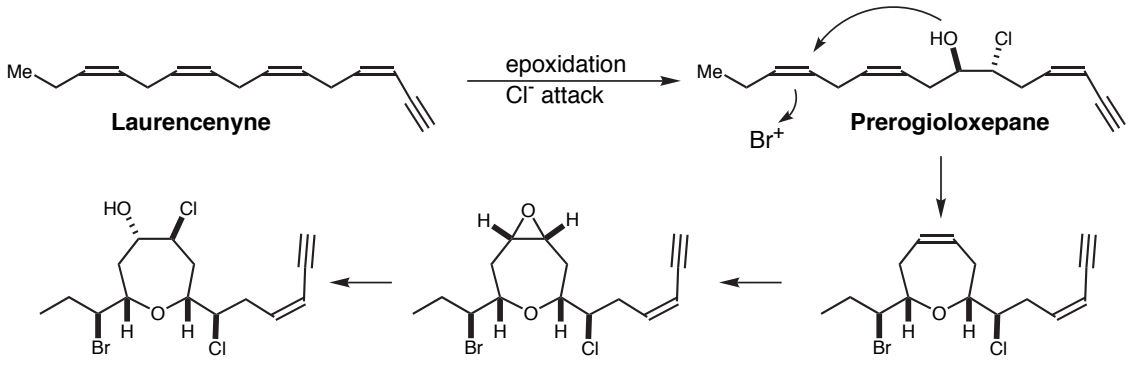
• Chlorine is incorporated by nucleophilic displacement as $Cl^-$ or through the reactions of alkenes with chloroperoxidases (CPO's), ie as "$Cl^+$"
• Bromine is almost exlusively incorproated as "$Br^+$" by bromoperoxidases (BrPO's)
• Iodoperoxidases have been identified, but not studied in as much detail as CPO and BrPO

*As a result, most halogen-bearing stereogenic centers occur as halohydrins or polycyclics!*

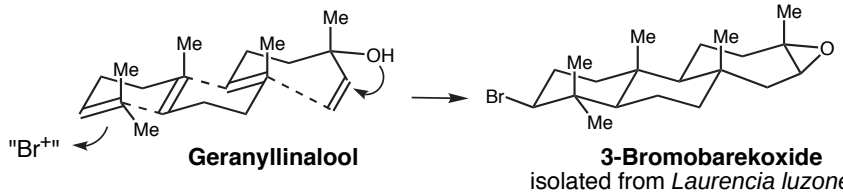



---

## *Examples of Halogen Biosynthesis*




Isolated from *Laurencia microcladia*




isolated from *Laurencia luzonensis*

Pietra, F., et al, *Helv. Chim. Acta*, **1992**, *75*, 310-322
Jefford, C. W. *Chem. Commun.*, **2000**, 1155-1156

## *Examples of Halogen Biosynthesis*

• The vast majority of the natural products herein discussed are isolated from the seaweeds (algae) of the genus *Laurencia* and *Plocamium.*
• Sea hares of the species *Aplysia* that feed on the seaweed are also sources of the natural products and can modify them

*Laurencia* seaweed

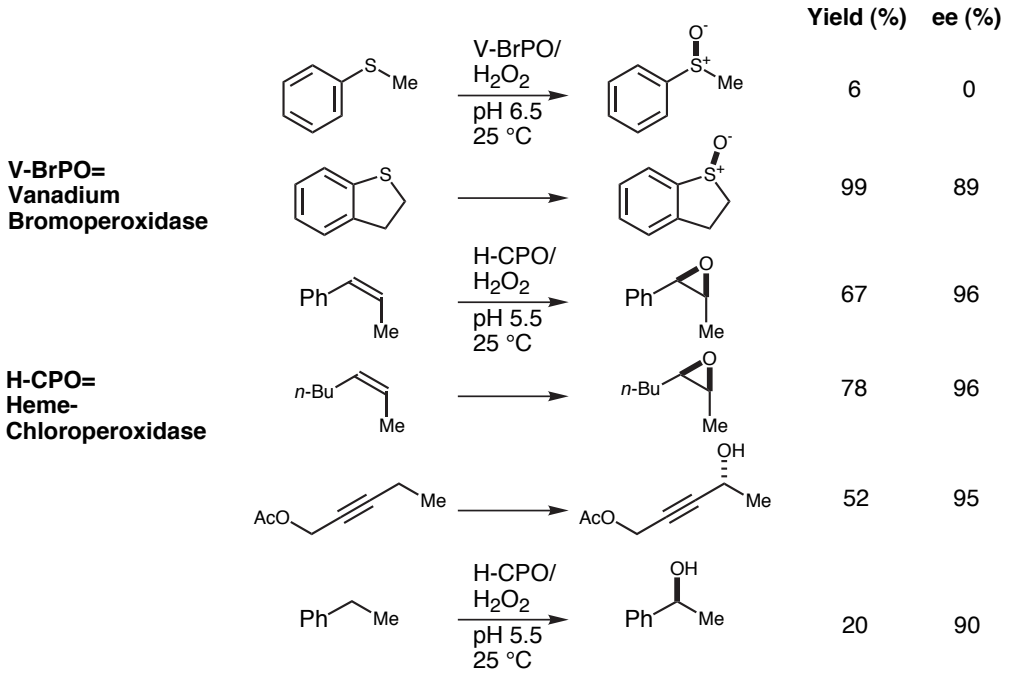
*Aplysia* sea hare




Faulkner, D. J., et al, *Comp. Biochem. Physiol.*, **1974**, *49B*, 37-41

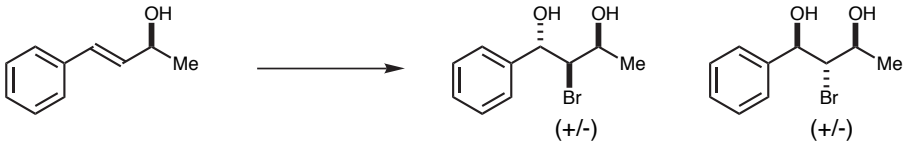
---

## *Haloperoxidases Catalyze Selective Oxidations*




***Sulfoxidation:*** Allenmark, A., et al, *J. Org. Chem.*, **1997**, *62*, 8455-8458
***Epoxidation:*** Hager, L. P. & Jacobsen, E. N., et al, *J. Am Chem. Soc.*, **1993**, *115*, 4415-4416
***Propargylic Oxidation:*** Hager, L. P. & Hu, S., *J. Am. Chem. Soc.*, **1999**, *121*, 872-873
***Benzylic Oxidation:*** Zaks, A., et al, *J. Am. Chem. Soc.*, **1995**, *117*, 10419-10424

## *Haloperoxidases Catalyze Unselective Bromohydrin Formation*



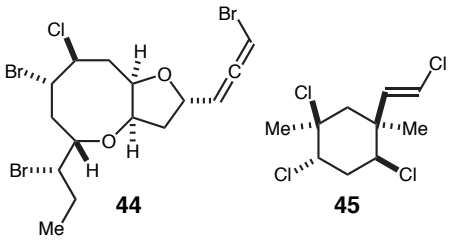

| | | |
|---|---|---|
| *N*-Bromoacetamide | 75% | 25% |
| H-CPO, $Br^-$, $H_2O_2$ | 61% | 39% |
| H-LPO, $Br^-$, $H_2O_2$ | - | - |
| V-BrPO, $Br^-$, $H_2O_2$ | 66% | 34% |

H-CPO=Heme-dependent chloroperoxidase from *Caldariomyces Fumago* (fungus)
H-LPO=Heme-dependent lactoperoxidase (haloperoxidase) from bovine milk
V-BrPO=Vanadium-dependent bromoperoxidase from *Corallina Officinalis* (marine algae)

Coughlin, P., et al, *Biotechnology Letters*, **1993**, *15*, 907-912

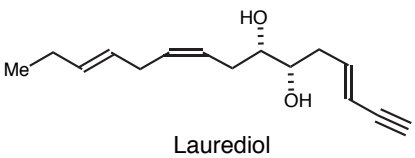
"One of the most interesting, yet unsolved problems in the area of marine biohalogenation, is the biogenesis of the chiral halogenated marine natural products."
Butler, A. *Chem. Rev.*, **1993**, *93*, 1937–1944.

"All haloperoxidases catalyze smooth, yet unselective chlorination, bromination or iodination of relatively electron-rich groups in organic compounds...However, there must be more stereo- and/or regioselective halogenating enzymes in nature, regarding the presence of halometabolites like **44** and **45**."
Franssen, M. C. R., *Catalysis Today*, **1994**, *22*, 441-457



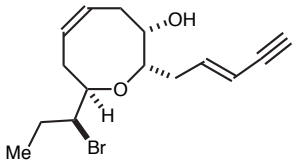

---

## *Enzyme-Catalyzed Bromohydrin Formation*

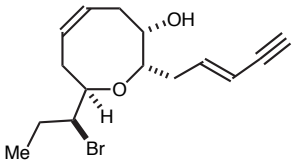



Laurediol

Lactoperoxidase;
NaBr, $H_2O_2$, pH 5.5
0.05% Yield
(0.41% BORSM)

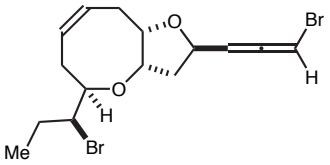



*E*-Prelauretin




*E*-Prelauretin

Lactoperoxidase;
NaBr, $H_2O_2$, pH 5.5
0.03% Yield
(0.19% BORSM)



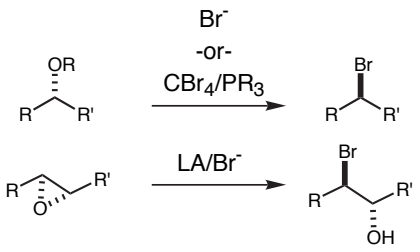

Laurallene

Murai, A., et al:
*Tetrahedron Lett.*, **1995**, *36*, 737-740
*Tetrahedron*, **1997**, *53*, 8371

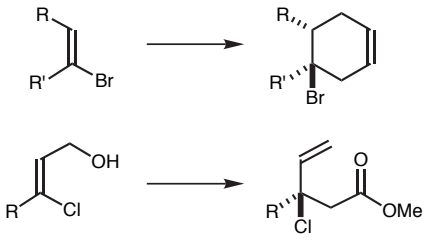
shaw 11/12 2/4/02 2:01 PM

# *Methods of Halogenation*

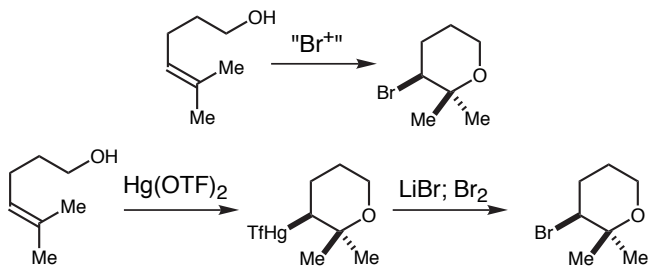
***Nucleophilic Displacement:***



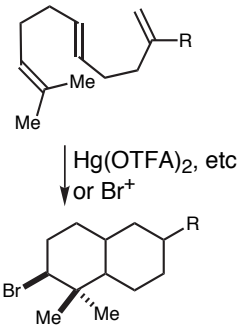

***Cycloaddition/Sigmatropic Rearrangement:***



***Bromoetherification/ Oxymercuration-Bromination***



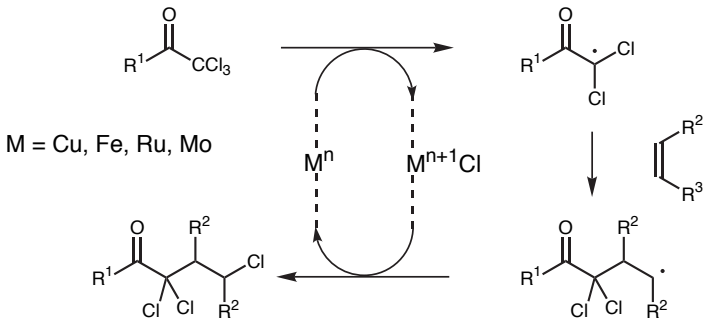

***Polyene Cyclization***

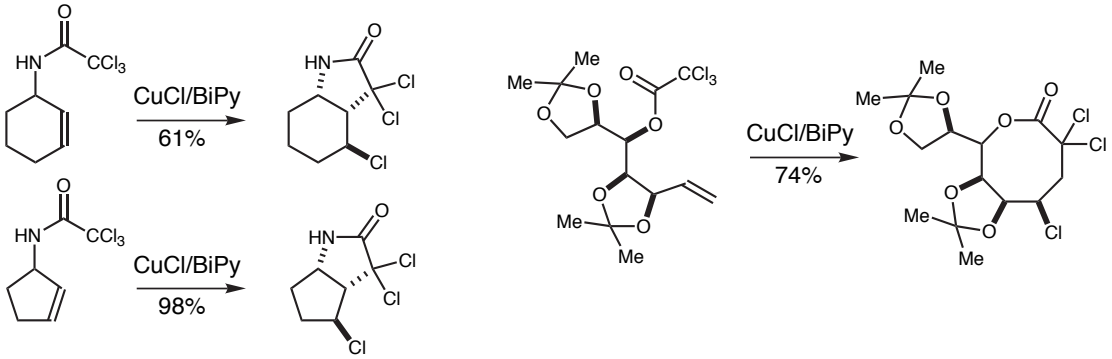



---

# *Methods of Halogenation*

***The Kharasch Reaction:***

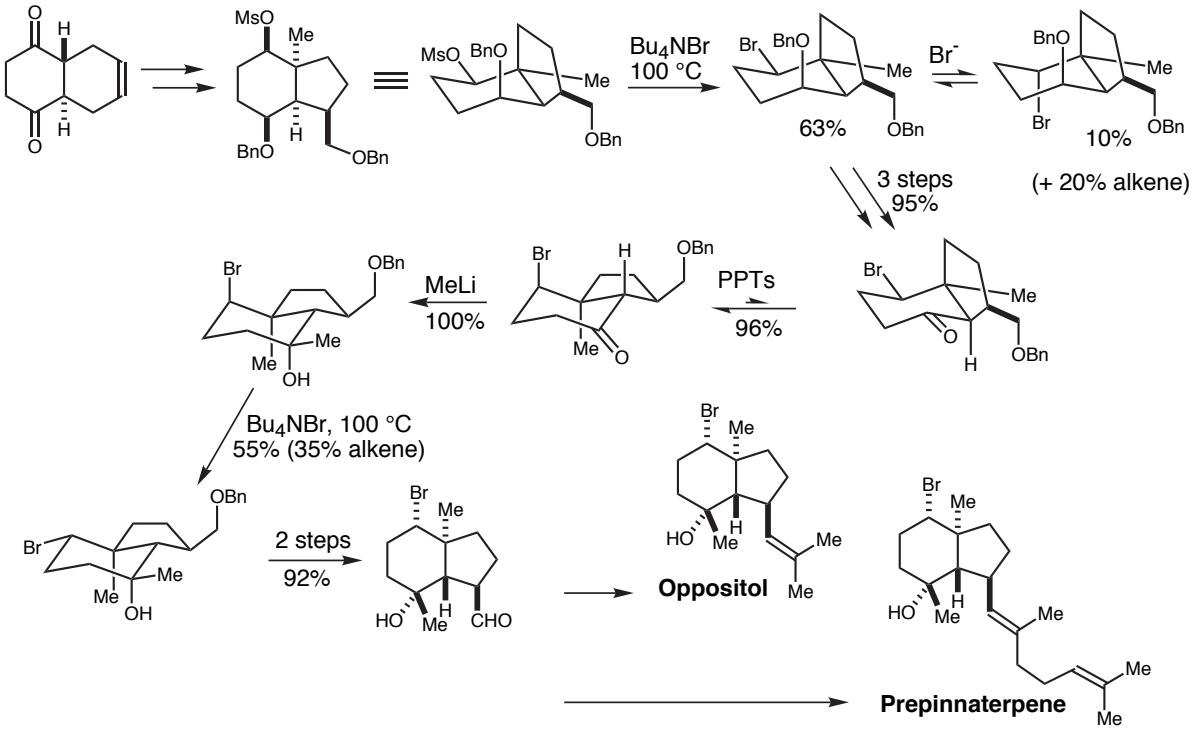




Weinreb, S. M., et al, *Tetrahedron*, **1988**, *44*, 4671-4678
Itoh, K., et al, *J. Org. Chem*, **1993**, *58*, 464-470
Speckamp, W. N., et al, *Synlett*, **1993**, 739

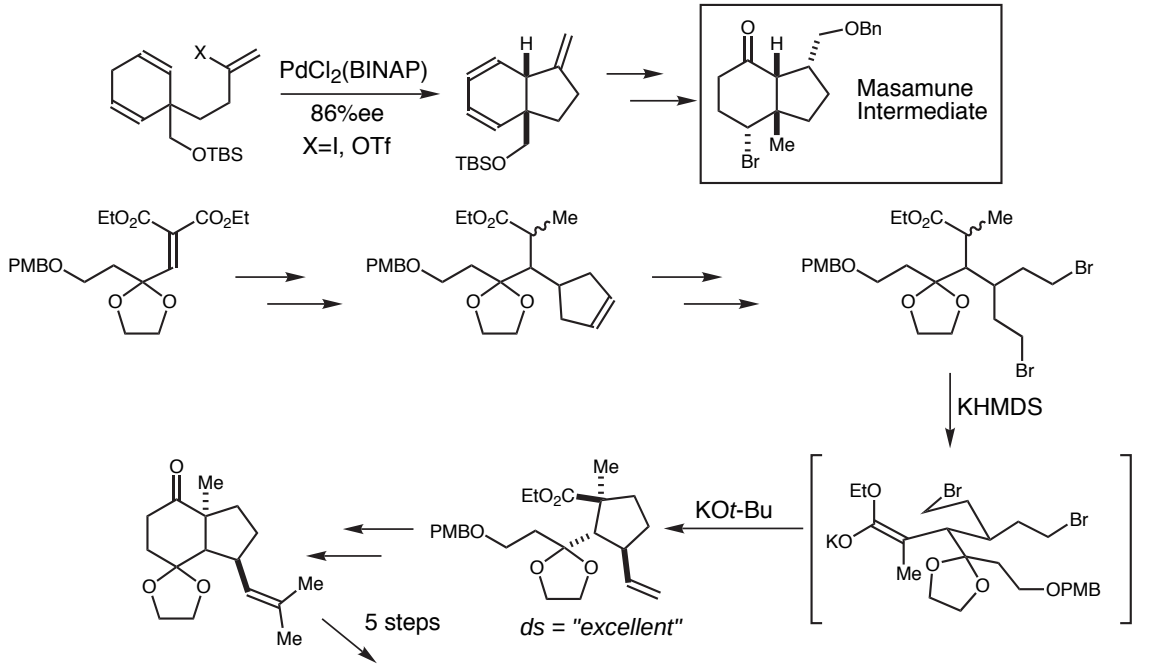
## *Synthesis of* Laurencia *Natural Products:*
## *T. Masamune's Prepinnaterpene & Oppositol*




Masamune, T., et al, *Tetrahedron Lett*, **1987**, *28*, 4303-4306

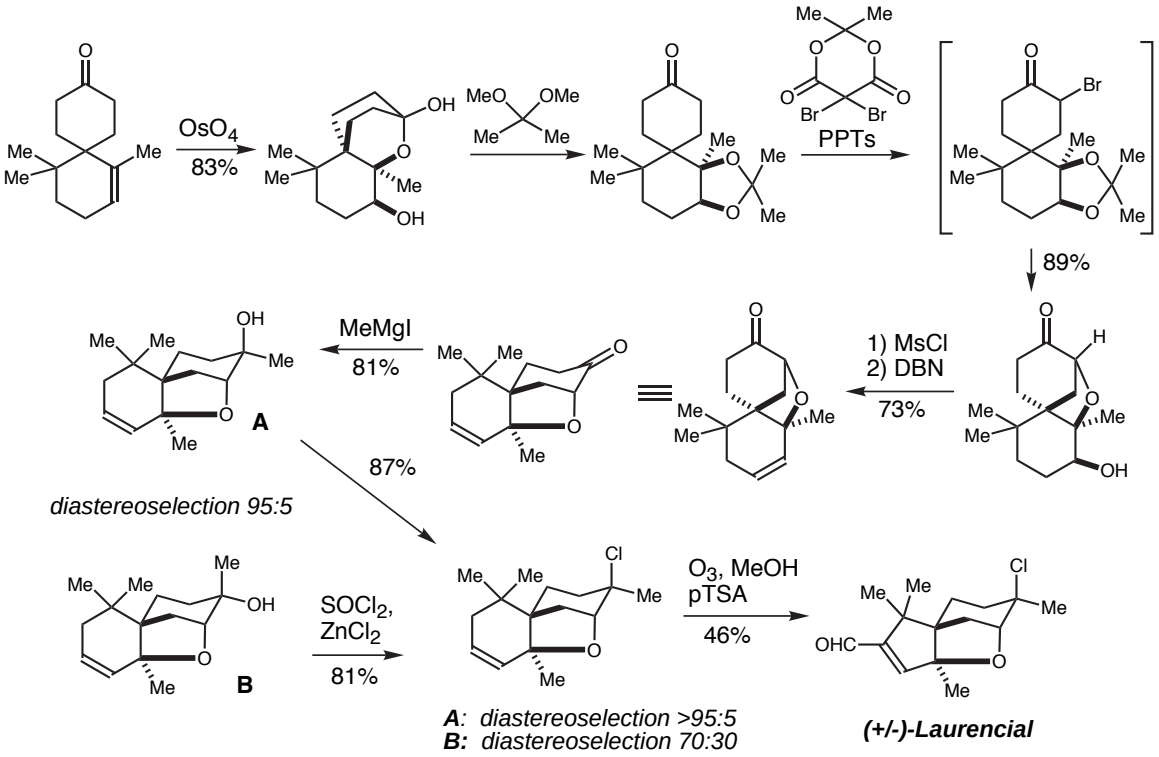
---

## *Synthesis of Prepinnaterpene & Oppositol:*
## *Improved Core Syntheses*




Shibasaki, M., et al, *Tetrahedron Asymm*, **1995**, *28*, 757-766
Kim, D., et al, *Tetrahedron Lett*, **1997**, *38*, 415-416

## *Synthesis of* Laurencia *Natural Products:*
## *Iwata's Laurencial*

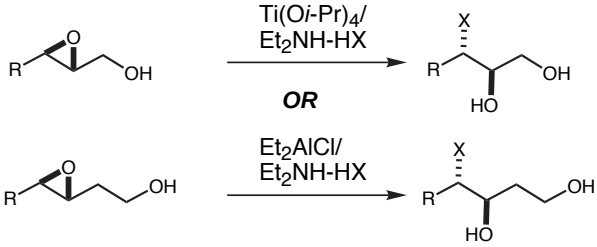



Iwata, C, et al, *Tetrahedron*, **1998**, *54*, 1396-1406

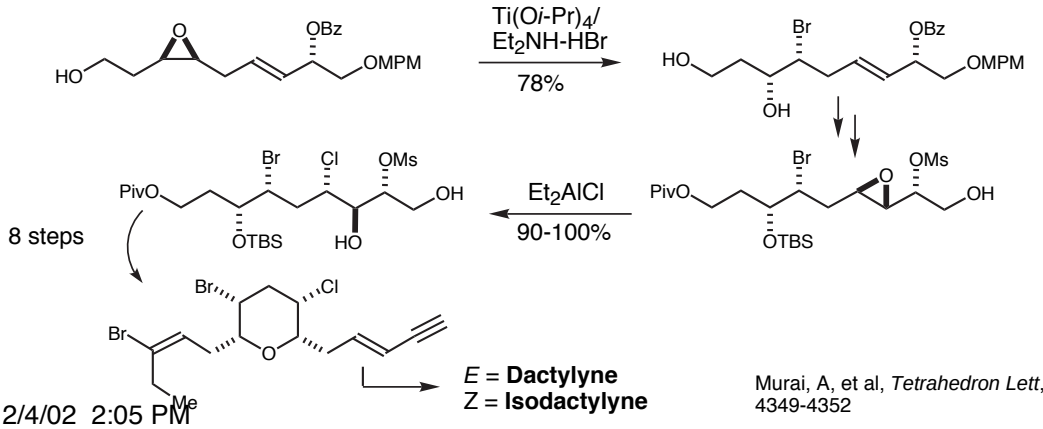
---

## *Synthesis of Dactylyne*

Murai's regioselective epoxy alcohol opening:




see also Sharpless, K. B., et al, *J. Org. Chem.*, **1985**, *50*, 15571560

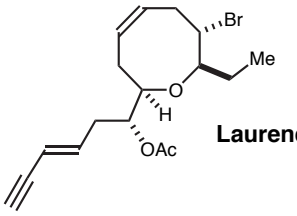



Murai, A, et al, *Tetrahedron Lett*, **1992**, *33*, 4349-4352

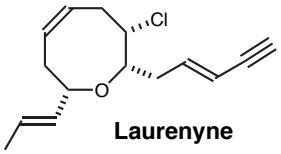
# *Synthesis of* Laurencia *Natural Products*

• Before the 1988 synthesis of Laurenyne by Overman, there was only one synthesis of an oxocane-containing natural product known, ie T. Masumune's synthesis of Laurencin in 0.003% yield.

• In the last decade, however, many syntheses of medium-ring ether natural products from the *Laurencia* series have appeared.




**Laurencin**

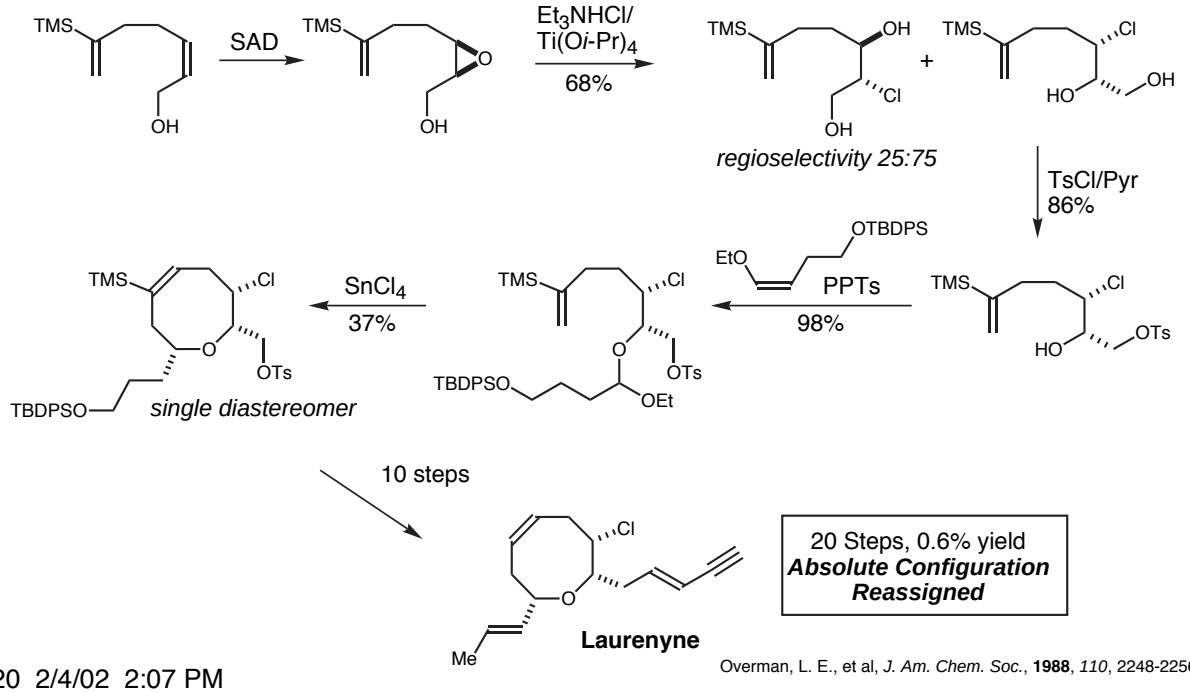



**Laurenyne**

**Principle Synthetic Challenges:**
1) medium ring formation
2) diastereoselectivity across ring
3) regiochemical control of unsaturation

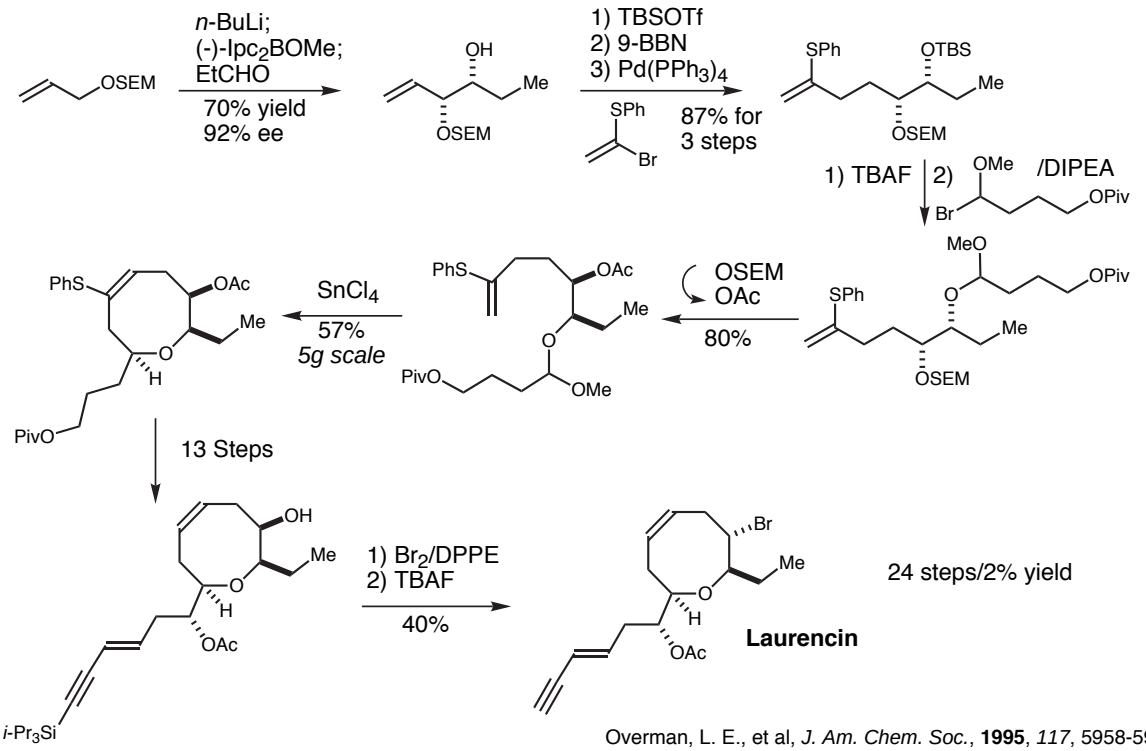
---

# *Overman's Synthesis of* Laurencia *Natural Products: Laurenyne*




Overman, L. E., et al, *J. Am. Chem. Soc.*, **1988**, *110*, 2248-2256

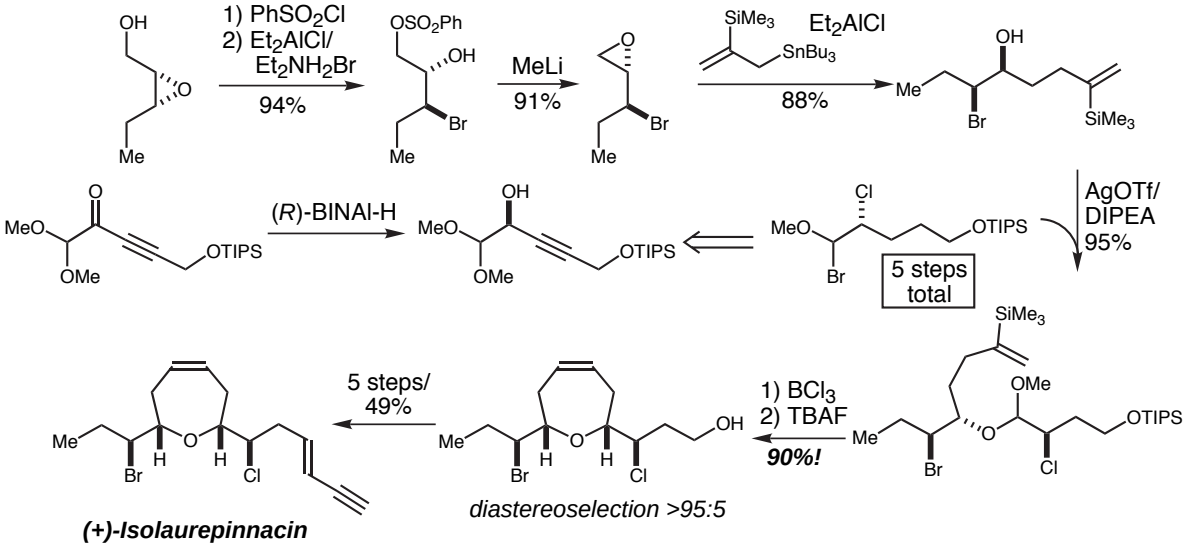
## *Overman's Synthesis of* Laurencia *Natural Products: Laurencin*




Overman, L. E., et al, *J. Am. Chem. Soc.*, **1995**, *117*, 5958-5966

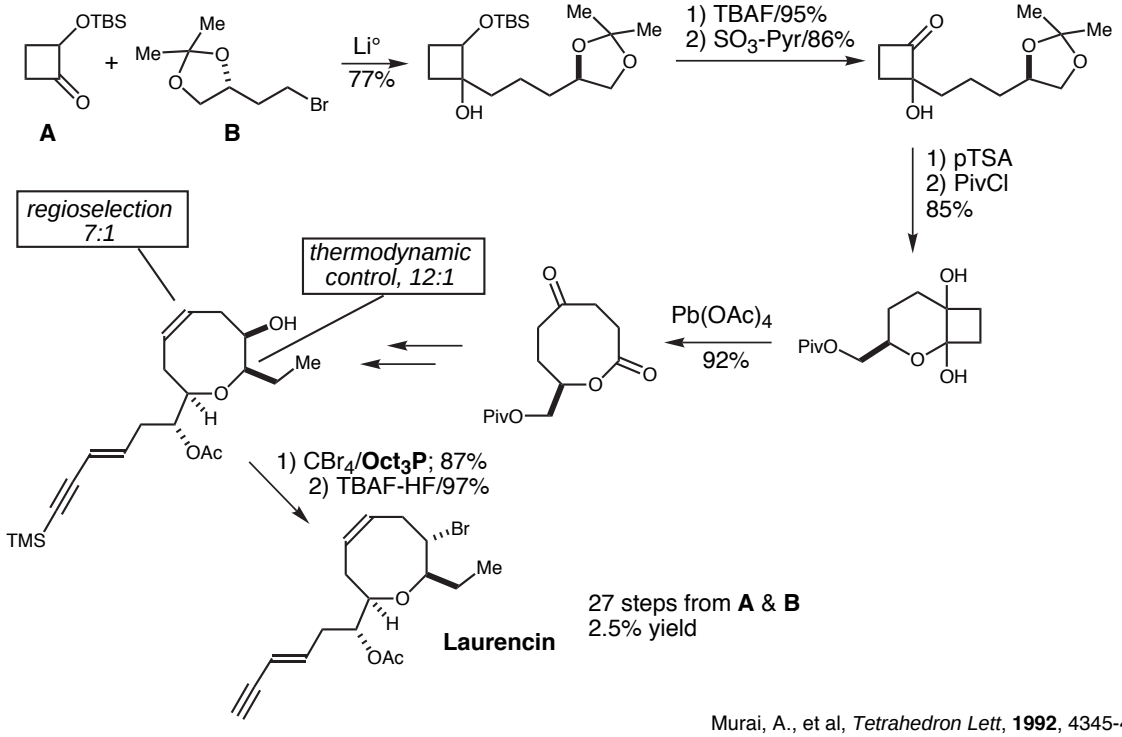
---

## *Overman's Synthesis of* Laurencia *Natural Products: Isolaurepinnacin*




Overman, L. E., et al, *J. Am. Chem. Soc.*, **1993**, *115*, 9305-9306

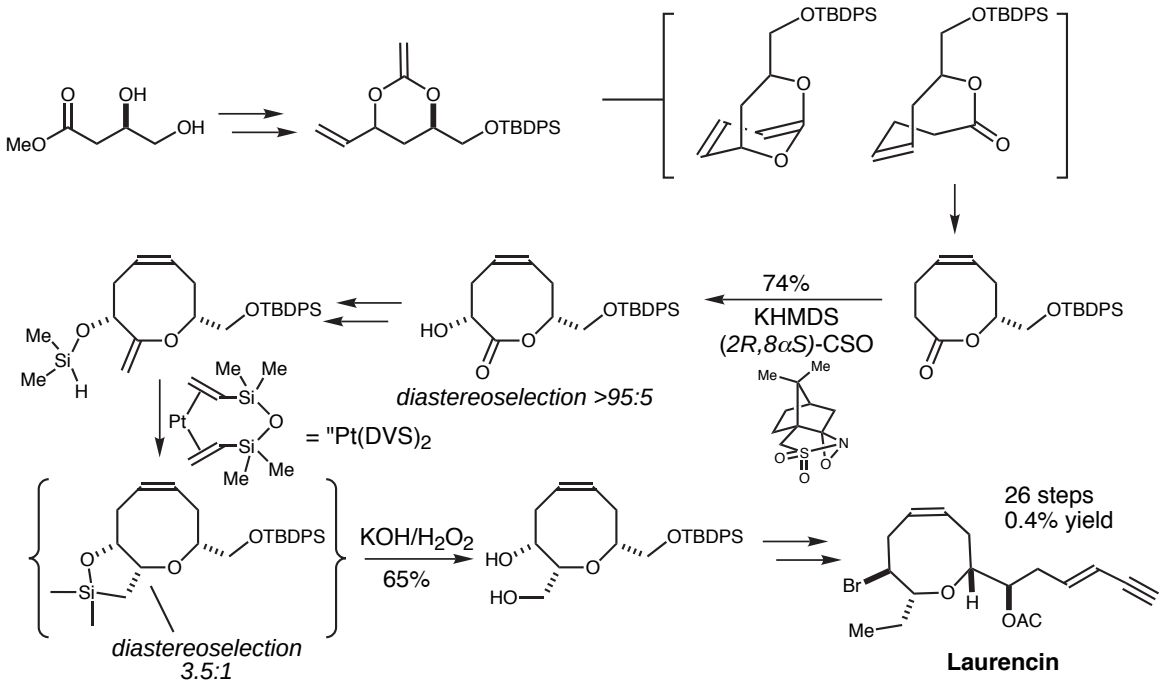
## *Murai's Synthesis of* Laurencia *Natural Products: Laurencin*




Murai, A., et al, *Tetrahedron Lett*, **1992**, 4345-4348

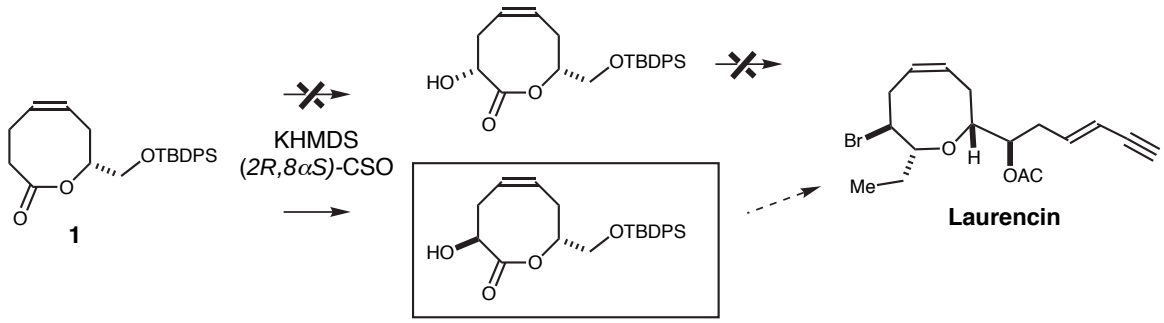
---

## *Synthesis of* Laurencia *Natural Products: Holmes & Clark's Laurencin*




Holmes, A. B., et al, *J. Am. Chem. Soc.*, **1993**, *115*, 10400-10401.

## *Synthesis of* Laurencia *Natural Products:*
## *Holmes & Clark's Laurencin - Retraction!*

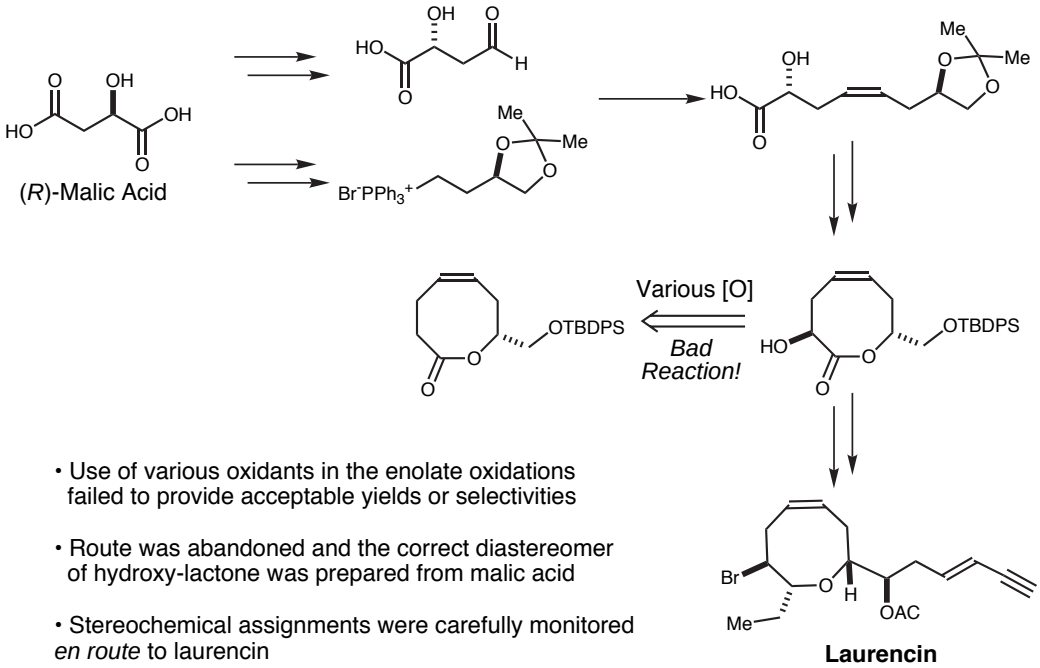



"The synthesis of lactone **1** as reported by J. S. Clark, Ph. D. Thesis, Cambridge University, 1988, is correct. The synthesis of (+)-laurencin in ref 1 is difficult to account for and must probably be charged to the fallibility of the other junior author and the gullibility of the senior author."

Holmes, A. B., et al, *J. Am. Chem. Soc.*, **1996**, *118, 6806.*

---

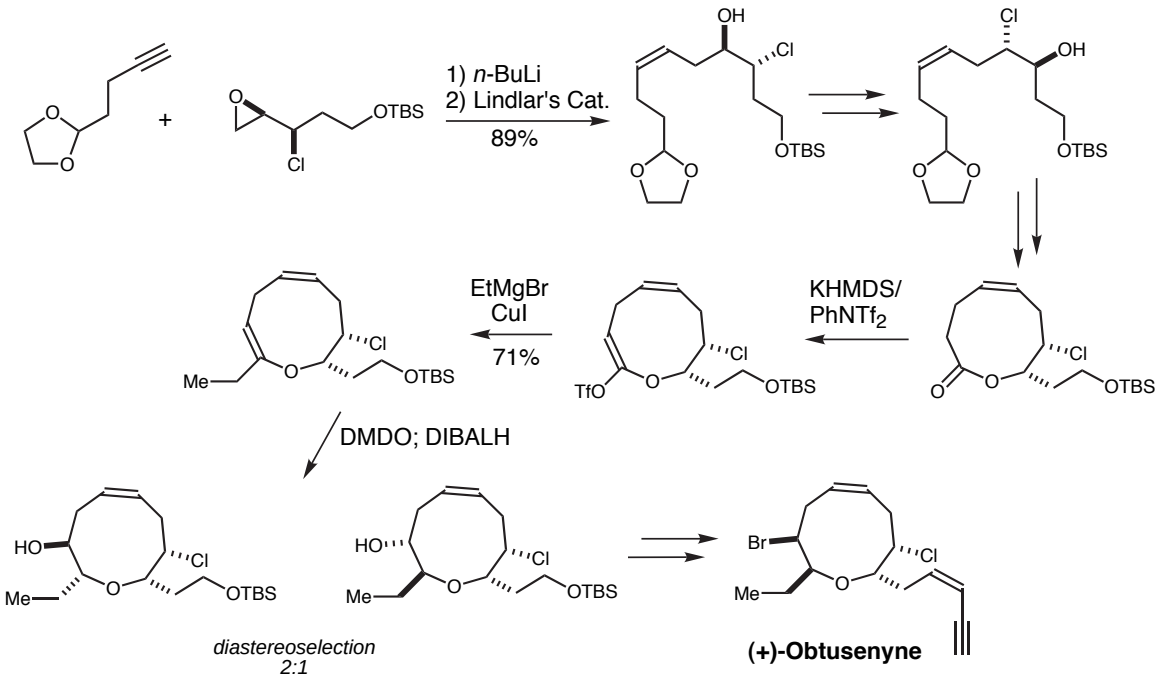
## *Synthesis of* Laurencia *Natural Products:*
## *Holmes & Clark's Laurencin - Retooled*




- Use of various oxidants in the enolate oxidations failed to provide acceptable yields or selectivities
- Route was abandoned and the correct diastereomer of hydroxy-lactone was prepared from malic acid
- Stereochemical assignments were carefully monitored *en route* to laurencin

Holmes, A. B., et al, *J. Am. Chem. Soc.*, **1997**, *119*, 7483-7498

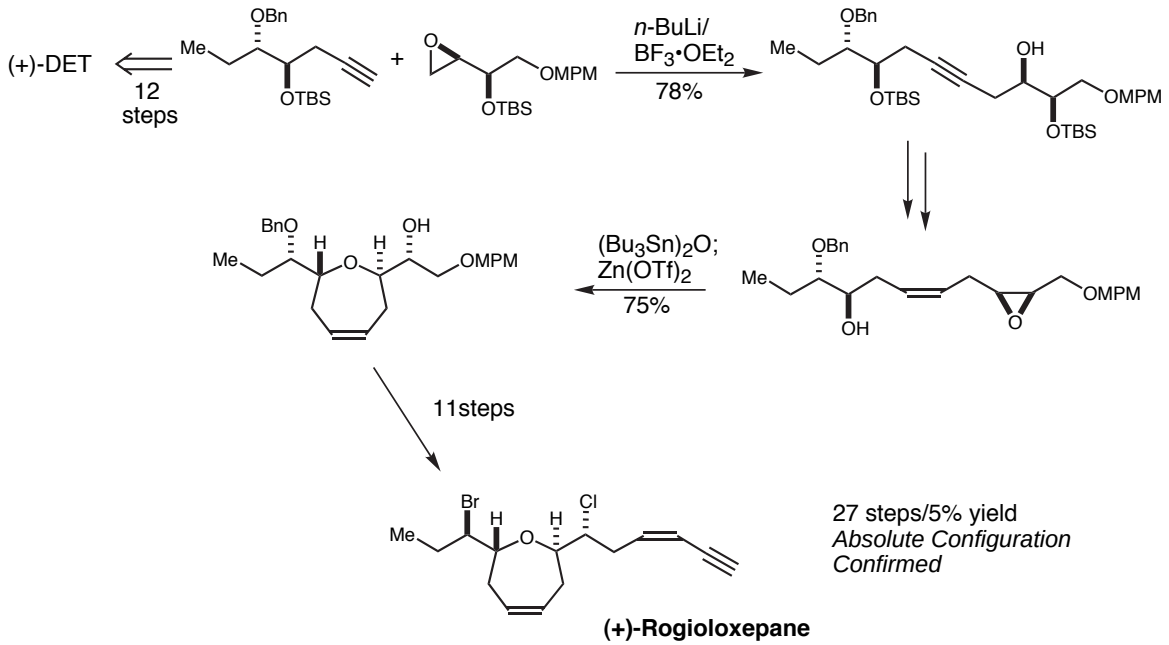
## *Synthesis of* Laurencia *Natural Products: Murai's Obtusenyne*




Murai, A., et al, *J. Org. Chem.*, **1999**, *64*, 2616-2617

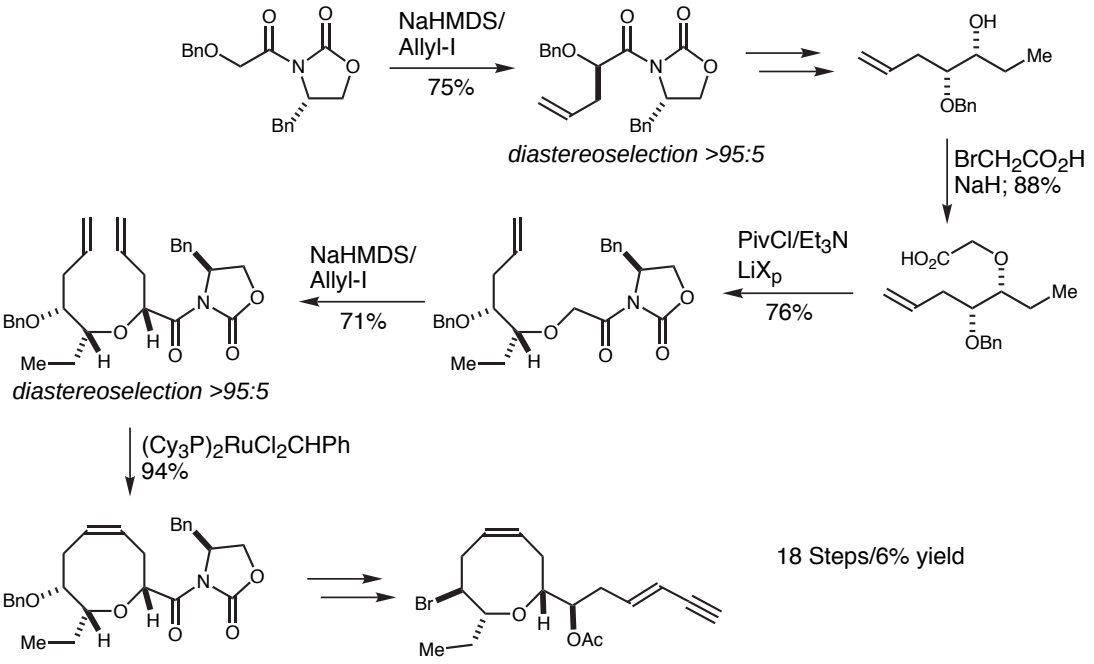
---

## *Synthesis of* Laurencia *Natural Products: Suzuki's Rogioloxepane A*




Suzuki, T., et al, *Tetrahedron Lett.*, **2001**, *42*, 1543-1546

## *Synthesis of* Laurencia *Natural Products: Crimmins' Laurencin*

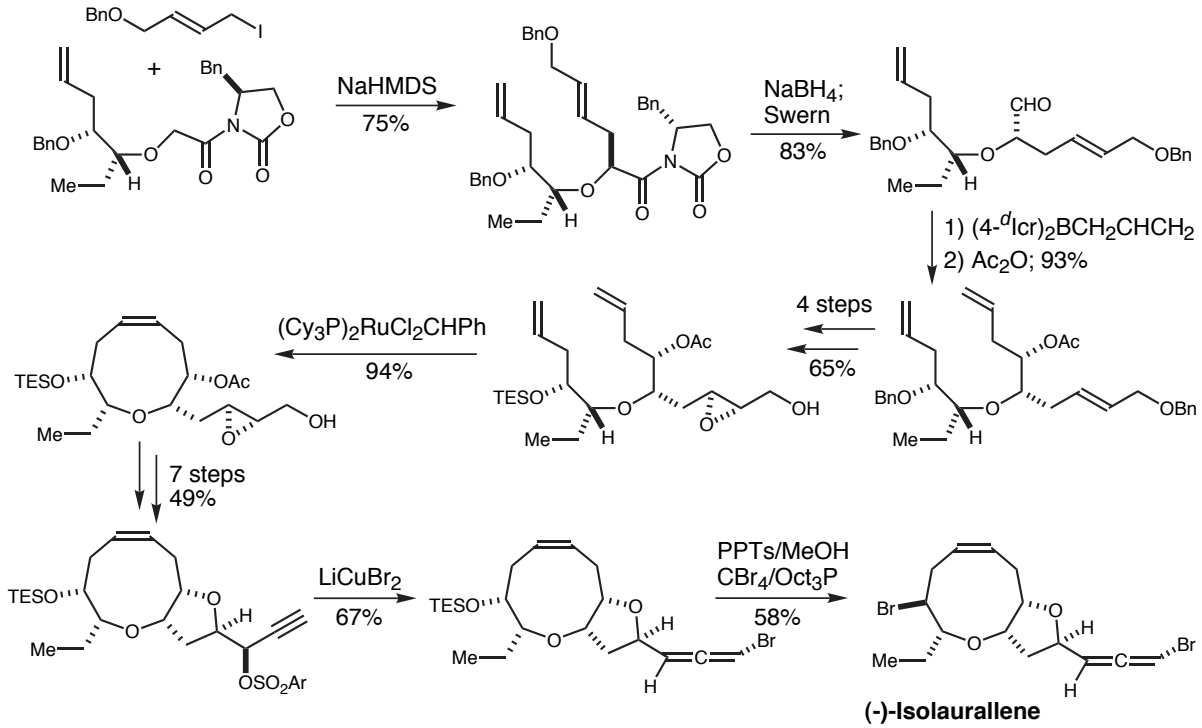



**Laurencin**

Crimmins, M. T., et al, *Org. Lett.*, **1999**, *1*, 2029-2032

---

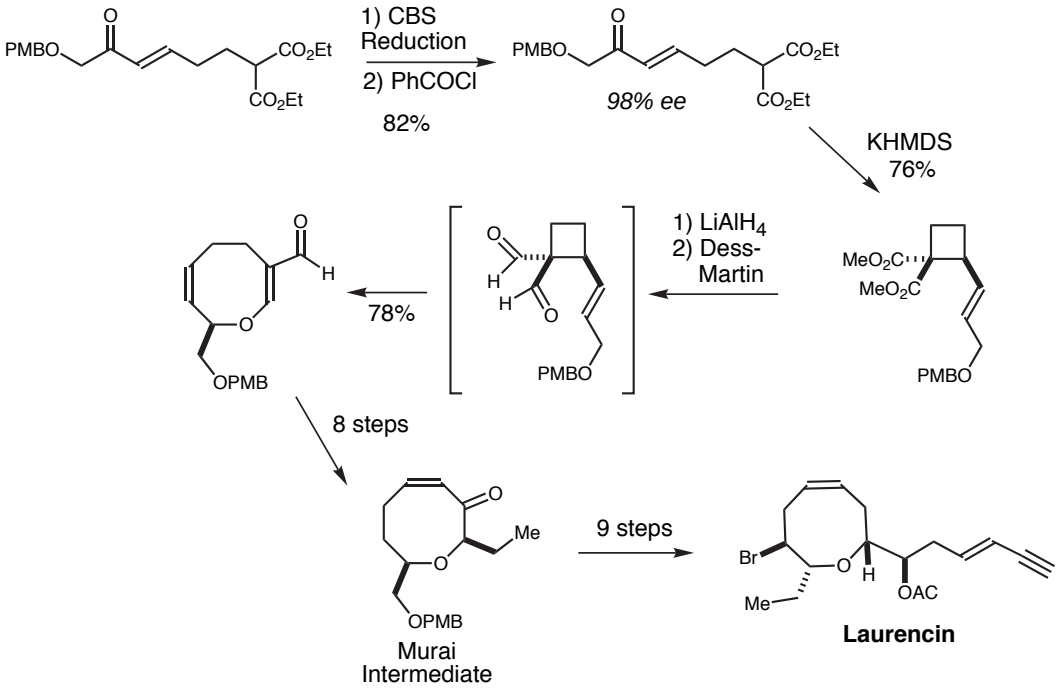
## *Synthesis of* Laurencia *Natural Products: Crimmins' Isolaurallene*




**(-)-Isolaurallene**

Crimmins, M. T., et al, *J. Am. Chem. Soc.*, **2001**, *123*, 1533-1534

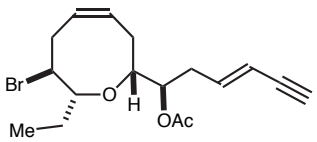
## *Boeckman's Laurencin*




Boeckman, R. K. Jr., et al, *Unpublished Results*

---

## *Synthesis of* Laurencia *Natural Products: Summary*




**Laurencin**

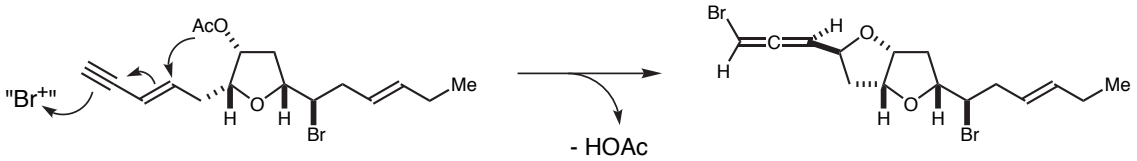
*Principle Synthetic Challenges:*

1) Medium Ring Ether Formation
2) Alkene Regiochemistry
3) Diastereoselectivity

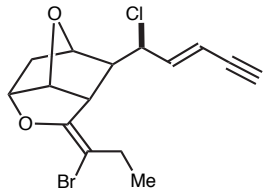
| | *year* | *ds across ring* | *rs of alkene* | *#steps* | *%yield* | *comments* |
|---|---|---|---|---|---|---|
| Overman | 1995 | >95:5 | >95:5 | 24 | 2 | good ds, general route |
| Murai | 1992 | 92:8 | 88:12 | >27 (30) | 2.5 | *first, but not best |
| Holmes | 1997 | 58:42 | >95:5 | >28 | 1.2 | good if claisen route panned out... |
| Boeckman | 2001 | - | - | 22 | 4 | Good 8-membered ring synthesis |
| Crimmins | 1999 | >99:1 | >95:5 | 18 | 6 | high yielding, general, but uses oxazolidinone auxiliary at **3** stages of the synthesis |

*"first" post-masamune

## *Synthesis of* Laurencia *Natural Products: Kumausyne & Kumausallene*




**Kumausyne** **Kumausallene**

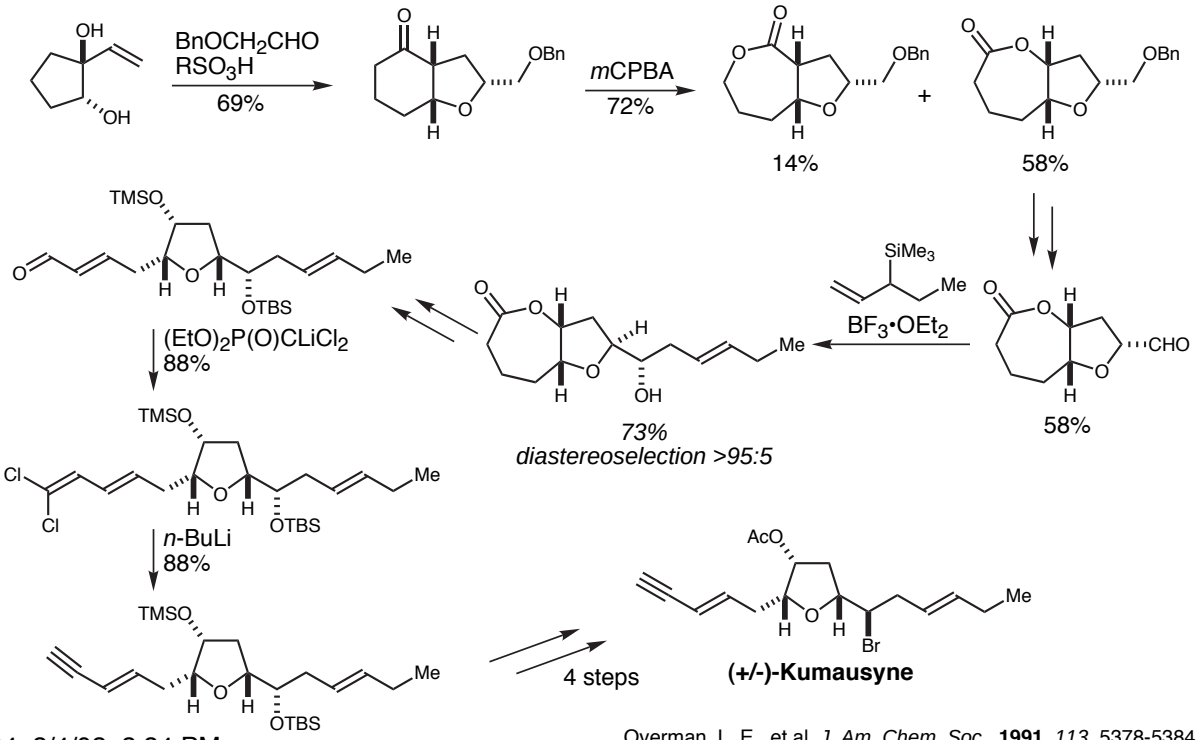



**(+/-)-*trans*-maneonene-B**

Holmes, A. B., et al, *Chem Comm*, **1984**, 1594-1595.

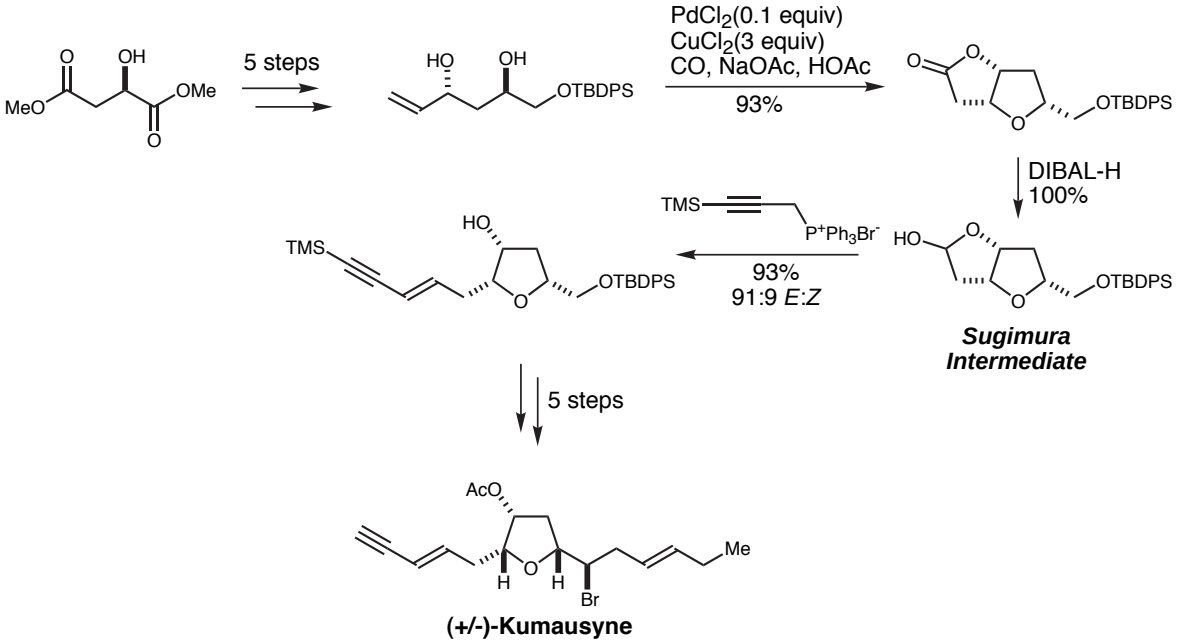
---

## *Synthesis of* Laurencia *Natural Products: Overman's Kumausyne*




Overman, L. E., et al, *J. Am. Chem. Soc.*, **1991**, *113*, 5378-5384

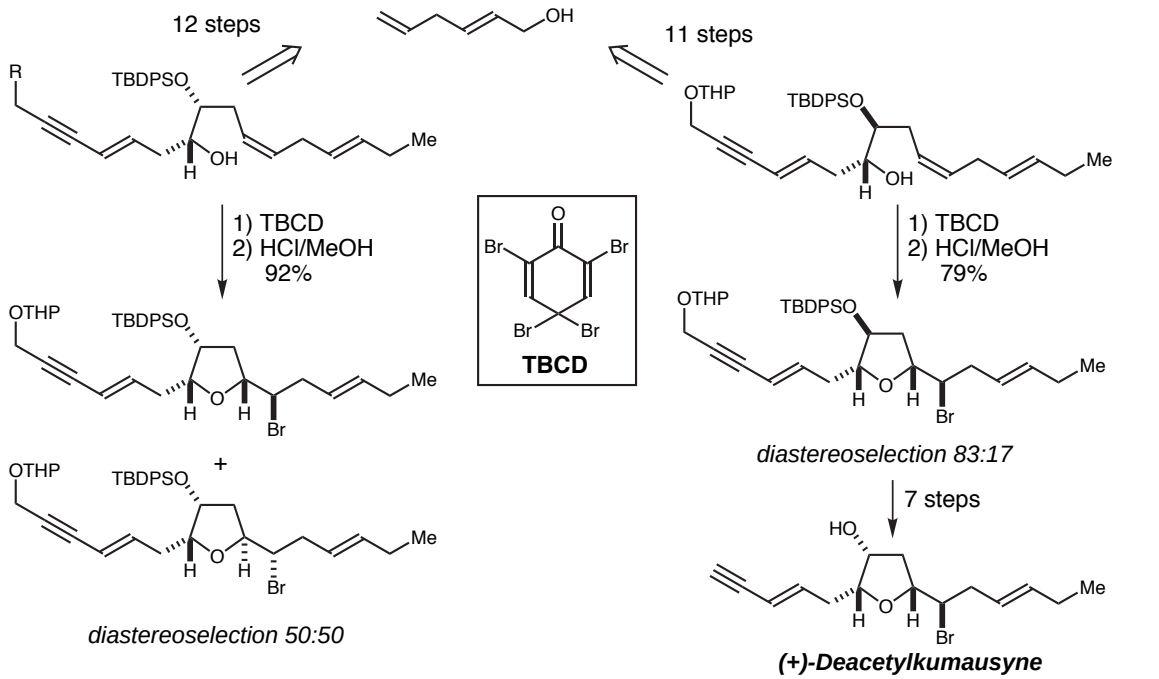
## *Synthesis of* Laurencia *Natural Products: Boukouvalas Kumausyne*




Boukouvalas, J., et al, *J. Org. Chem.*, **1998**, *63*, 916-917

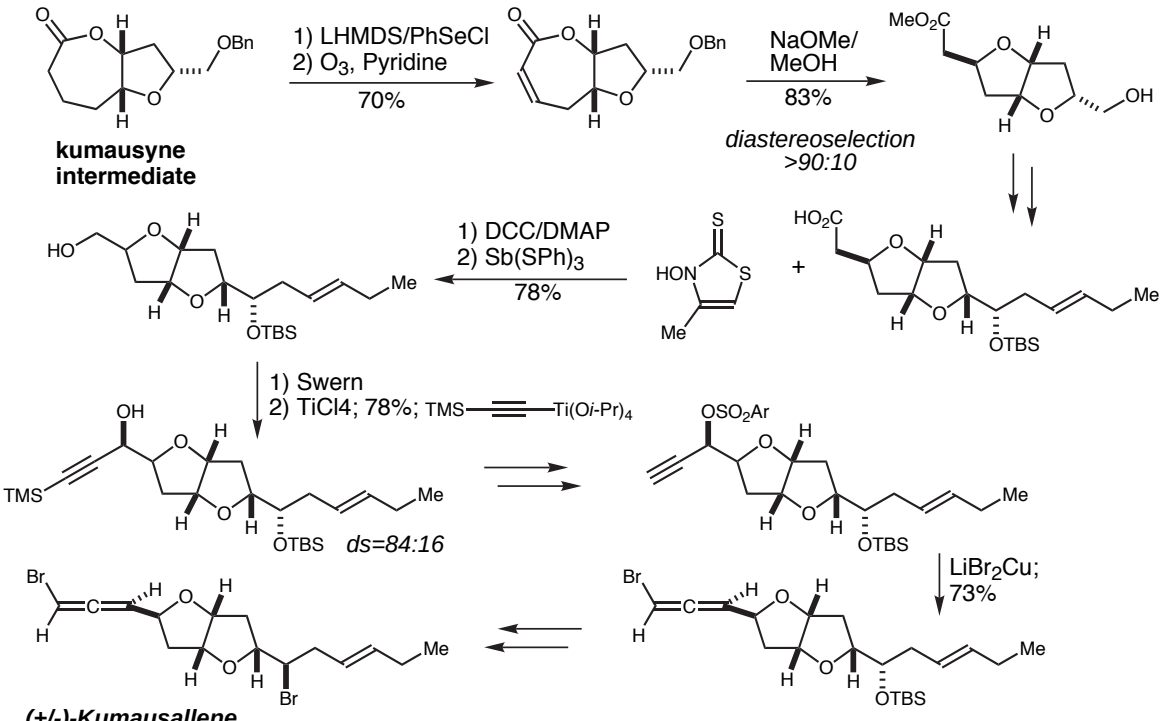
---

## *Synthesis of* Laurencia *Natural Products: Martín's Biomimetic synthesis of Kumausyne*




Martín, V. S., et al, *J. Org. Chem.*, **1997**, *62*, 1570-1571

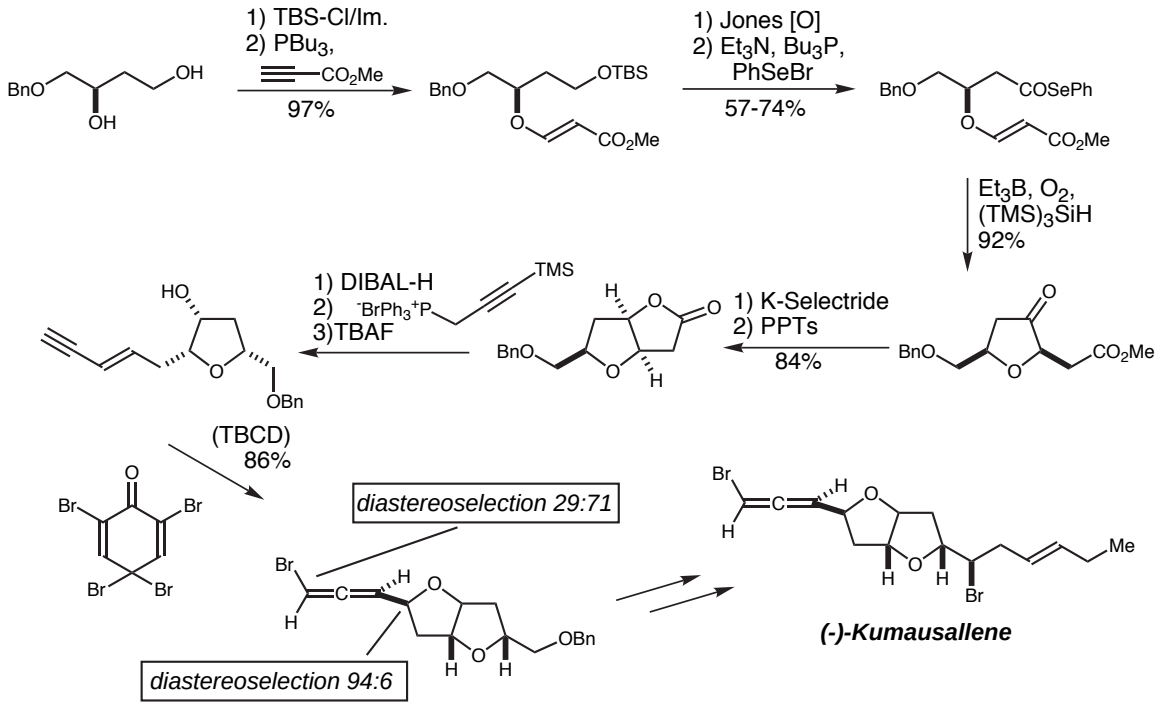
## *Synthesis of* Laurencia *Natural Products: Overman's Kumausallene*




Overman, L. E., et al, *J. Org. Chem.*, **1993**, *58*, 2468-2477

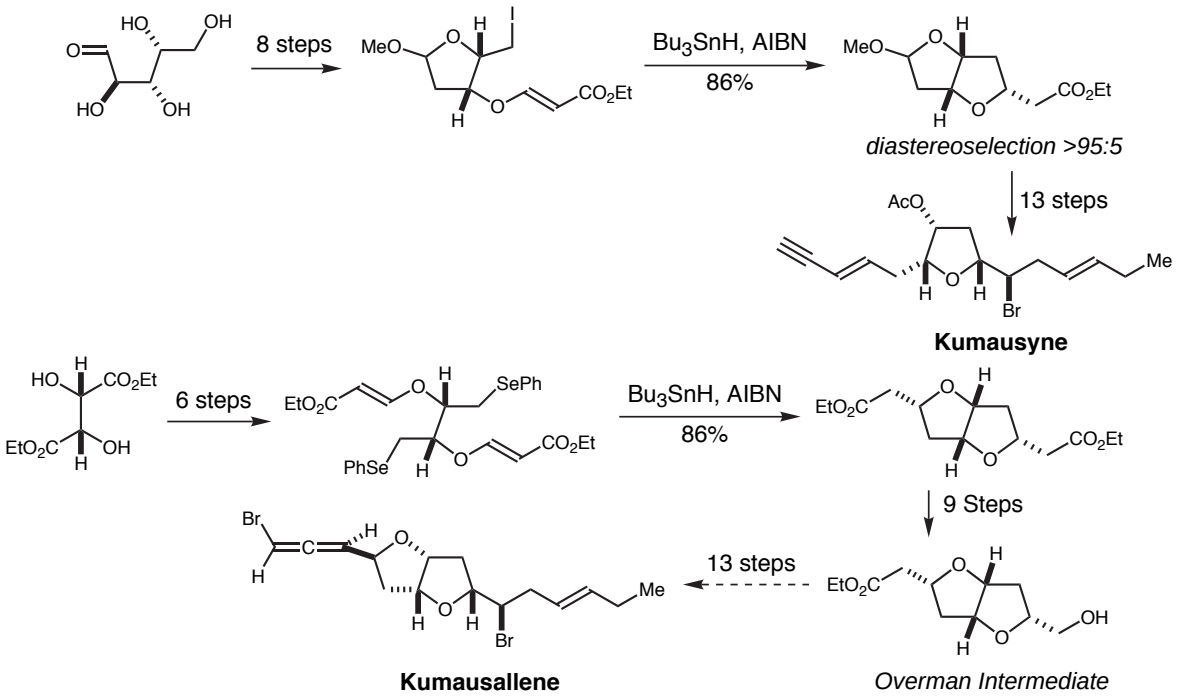
---

## *Synthesis of* Laurencia *Natural Products: Evans' Kumausallene*




Evans, P. A., et al, *Angew. Chem. Int. Ed.*, **1999**, *38*, 3175-3177

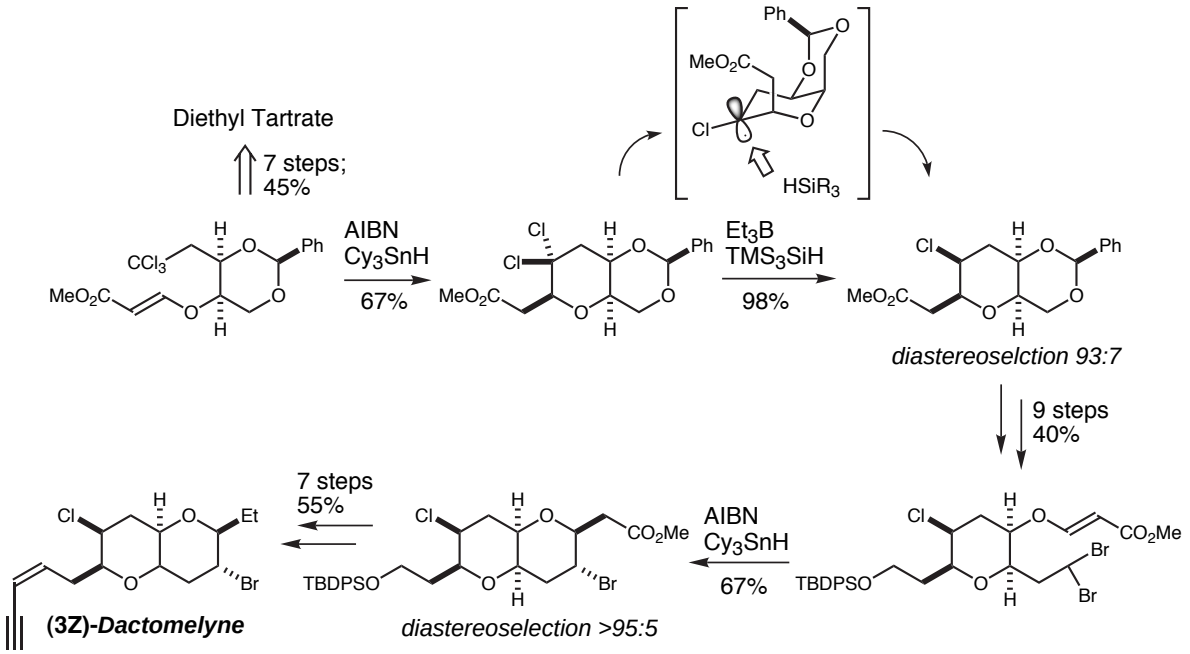
## *Synthesis of* Laurencia *Natural Products: Lee's Kumausyne & Kumausallene*




Lee, E, et al, *Tetrahedron Lett*, **1997**, *38*, 7757-7758
Lee, E, et al, *Tetrahedron Lett*, **1998**, *39*, 317-318

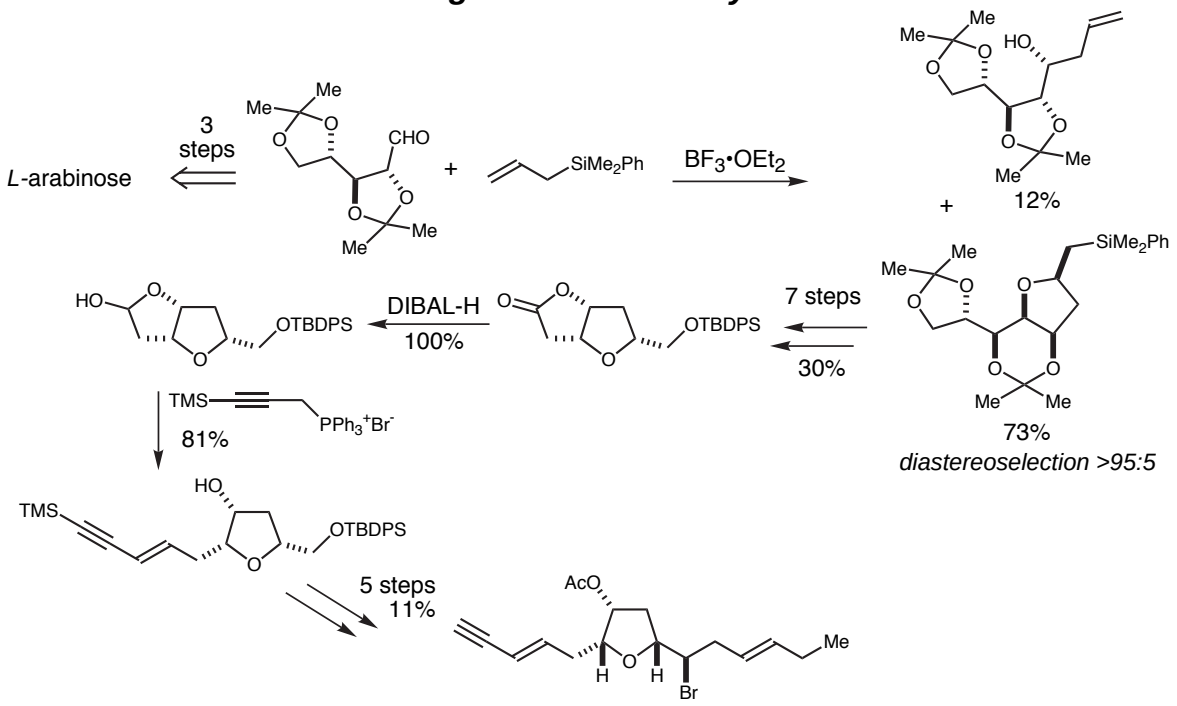
---

## *Synthesis of* Aplysia *Natural Products: Successful Application of Lee's Radical Methodology*




Lee, E, et al, *J. Am. Chem. Soc.* , **1995**, *117*, 8017-8017

## *Synthesis of* Laurencia *Natural Products: Sugimura's Kumausyne*

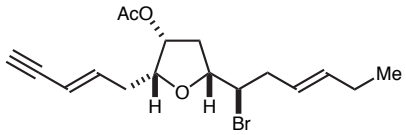



**Kumausyne**

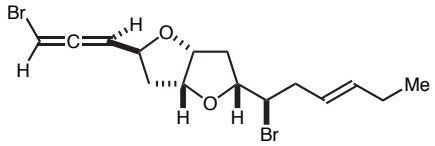
Sugimura, H., et al, *Tetrahedron Lett*, **1995**, *38*, 5789-5792

---

## *Synthesis of* Laurencia *Natural Products: Summary of Kumausyne and Kumausallene*



**Kumausyne**

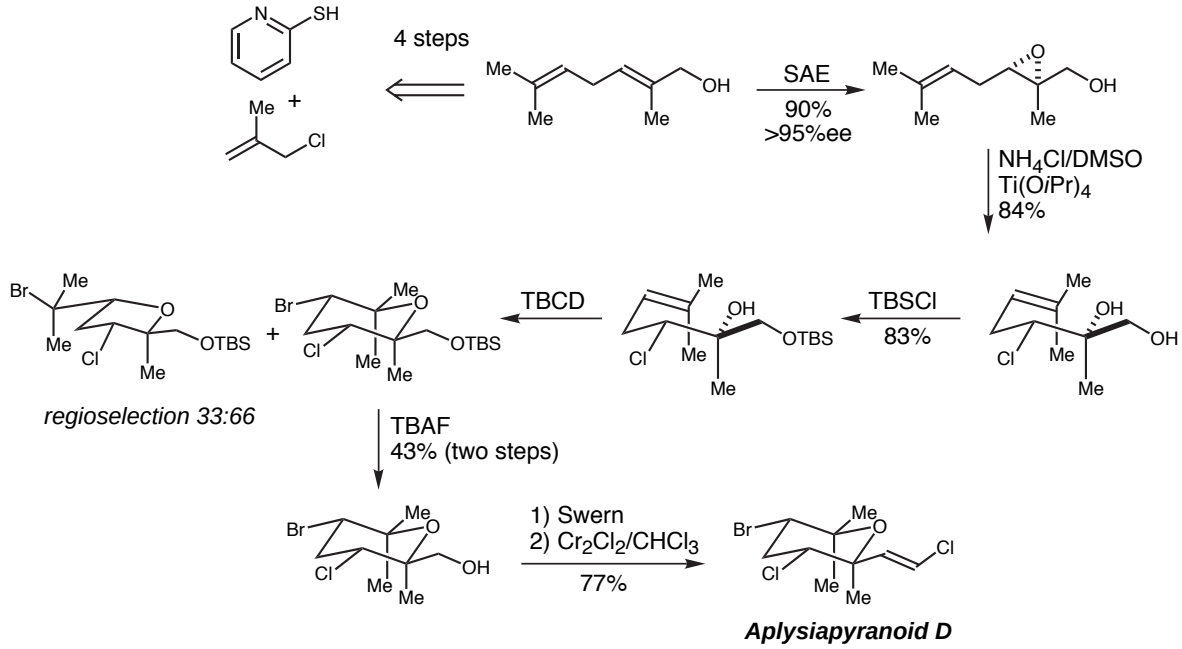


**Kumausallene**

| | year | #steps/%yield |
|---|---|---|
| **Overman** | **1991** | **13/5.4** |
| Sugimura | 1995 | 16/1.3 |
| Lee | 1997 | 17/2.5 |
| Martín | 1997 | 21/13 |
| **Boukoulavas** | **1998** | **13/6.2** |

| | year | #steps/%yield |
|---|---|---|
| **Overman** | **1993** | **17/2** |
| Lee | 1998 | 29/0.4 |
| **Evans** | **1998** | **14/6** |

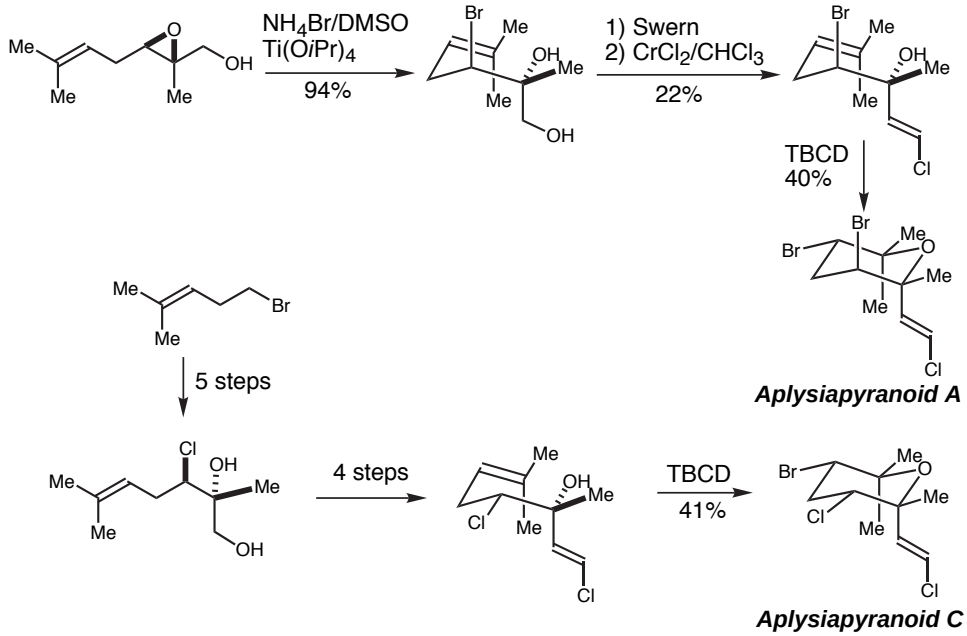
## *Synthesis of* Aplysia *Natural Products: Jung's Aplysiapyranoid D*




Jung, M. E., et al, *J. Org. Chem.*, **1992**, *56*, 1347-1348

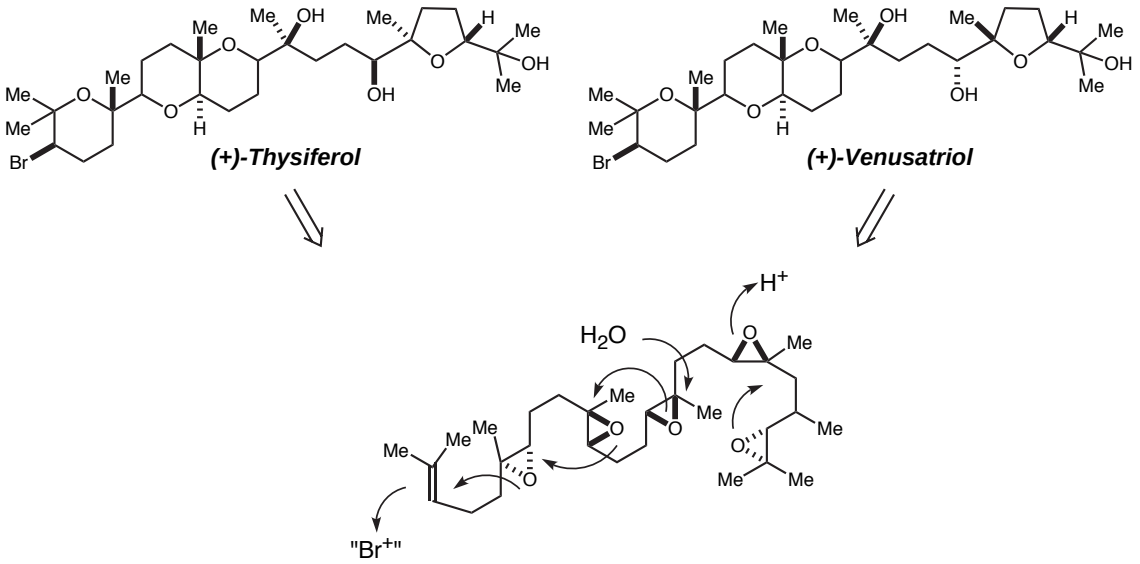
---

## *Synthesis of* Aplysia *Natural Products: Jung's Aplysiapyranoids A & C*



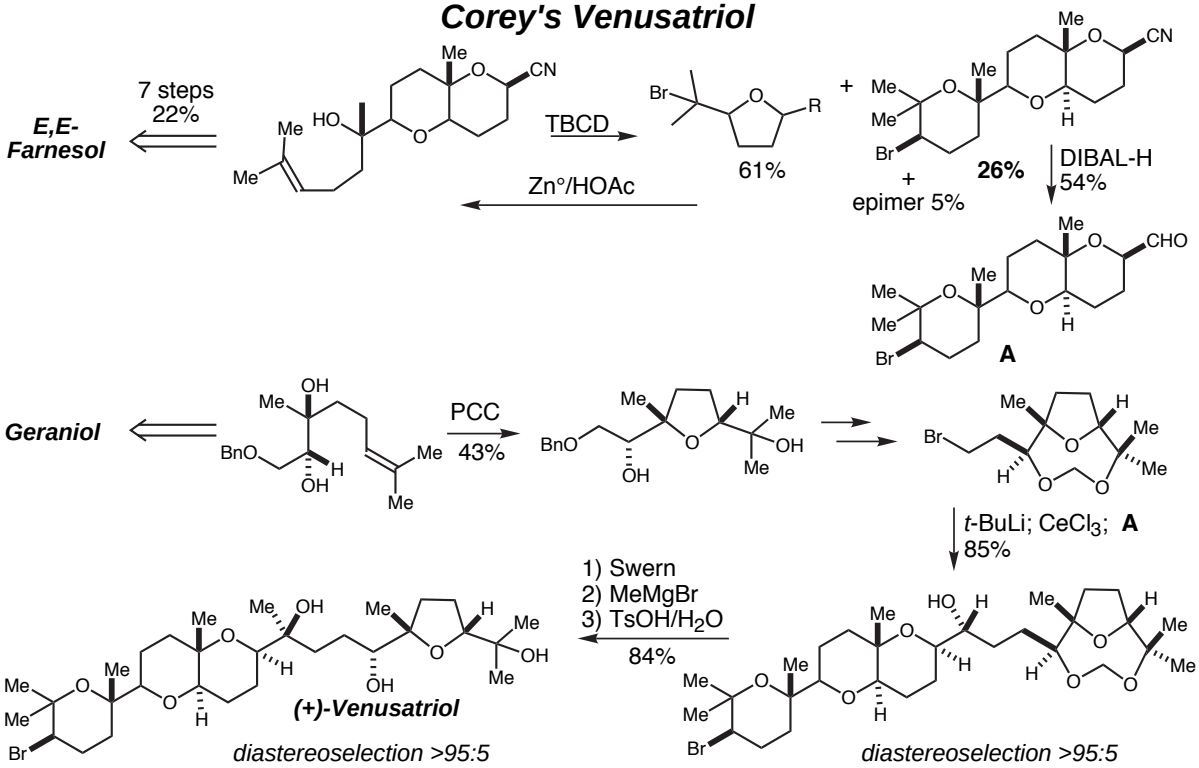

Jung, M. E., et al, *Tetrahedron Lett.*, **1993**, *34*, 923-926
Jung, M. E., et al, *J. Org. Chem.*, **1998**, *63*, 2982-2987

## *Synthesis of* Laurencia *Natural Products: Thyrsiferol & Venusatriol*



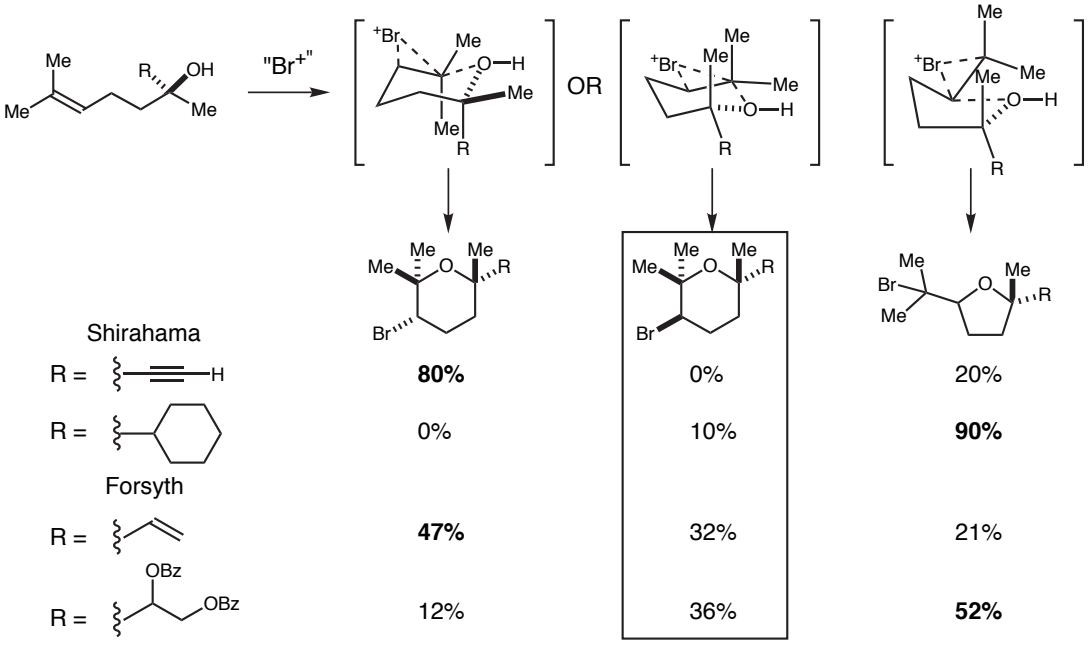

---

## *Synthesis of* Laurencia *Natural Products: Corey's Venusatriol*




Corey, E. J., et al, *Tetrahedron Lett.*, **1988**, *26*, 3171-3174

## *Synthesis of* Laurencia *Natural Products: Shirahama and Forsyth Improve the Bromocyclization*

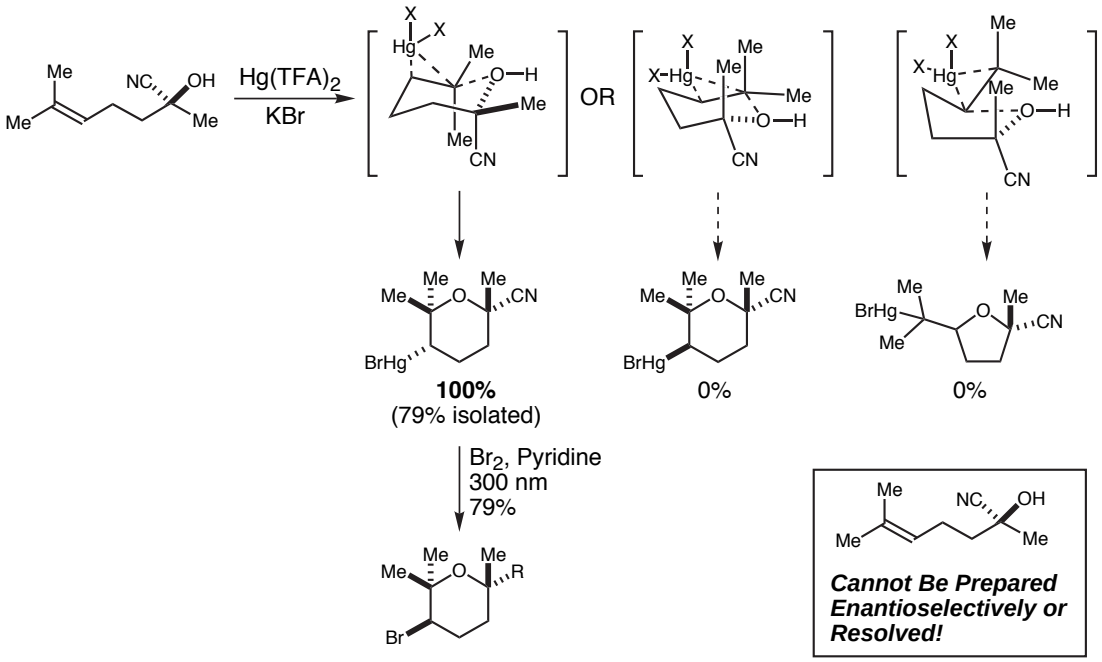



• Bulky R favors correct diastereomer, but also favors THF formation


Shirahama, H., et al, *J. Org. Chem.*, **1990**, *55*, 5088-5107
Forsyth, C. J., et al, *J. Am. Chem. Soc*, **2000**, *122*, 9099-9108

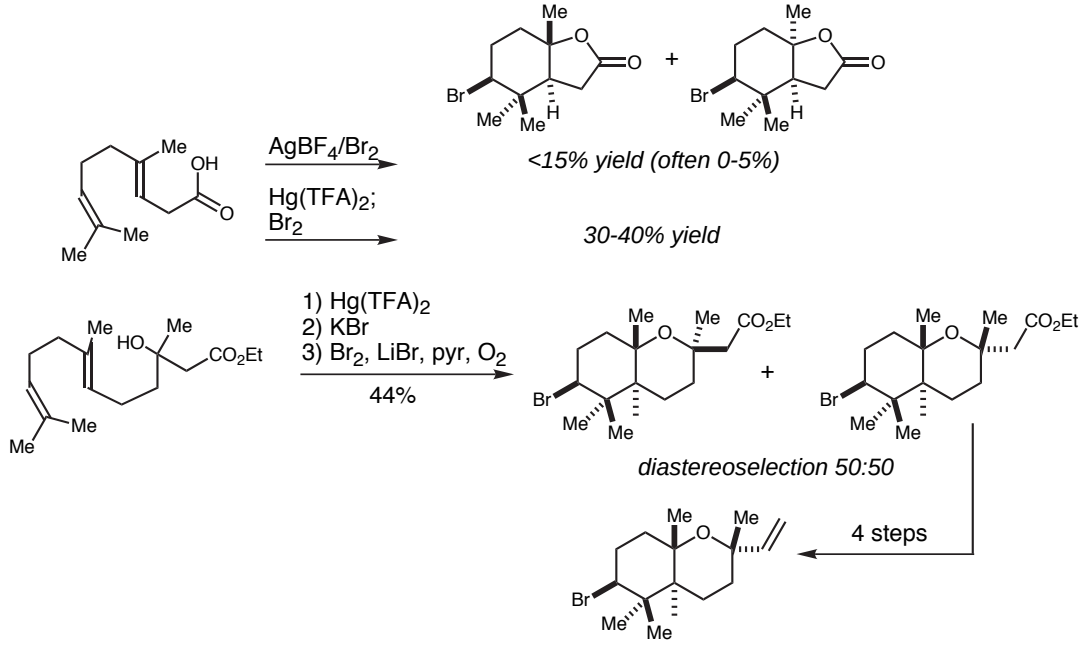

---

## *Synthesis of* Laurencia *Natural Products: Forsyth's Oxymercuration as an alternative*




***Cannot Be Prepared Enantioselectively or Resolved!***

## *Synthesis of* Aplysia *Natural Products: Hoye's Polycyclization*



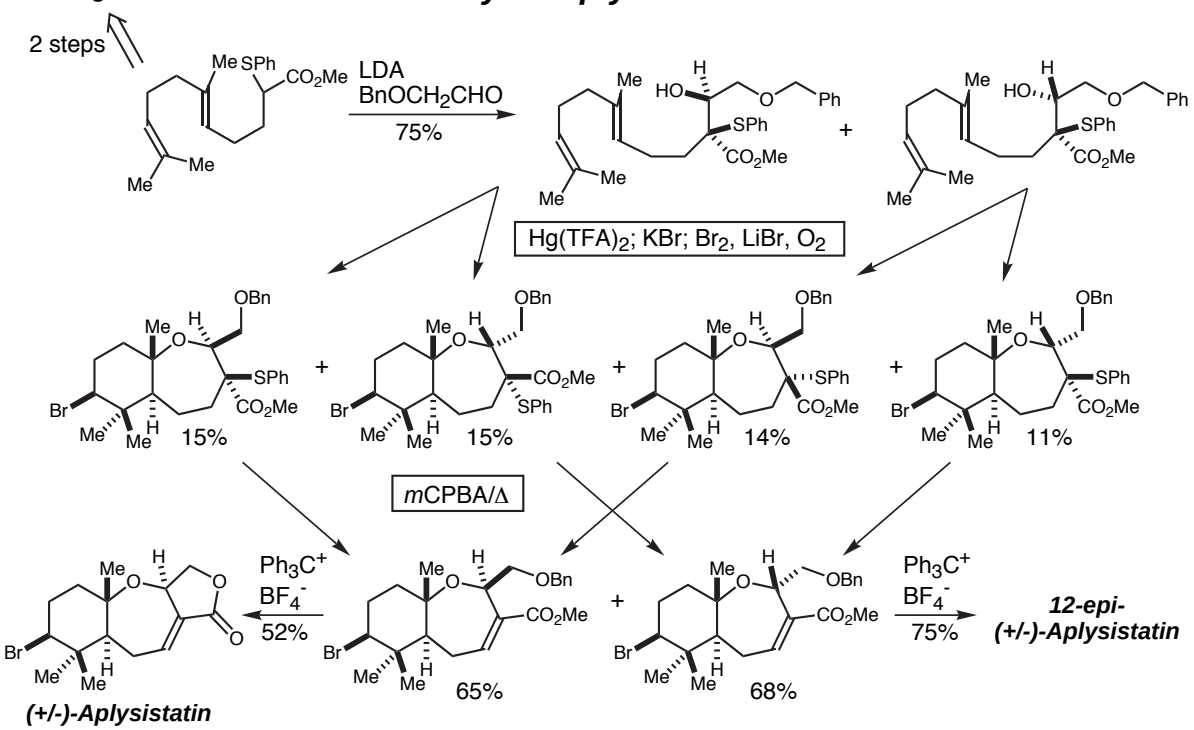

**dl-*3β-Bromo-8-epicaparappi Oxide***


Hoye, T. R., et al, *J. Org. Chem.*, **1978**, *48*, 3693-3697
Hoye, T. R., et al, *J. Org. Chem.*, **1979**, *49*, 3461-3467


---

## *Synthesis of* Aplysia *Natural Products: Hoye's Aplysistatin*

***Homogeraniol***

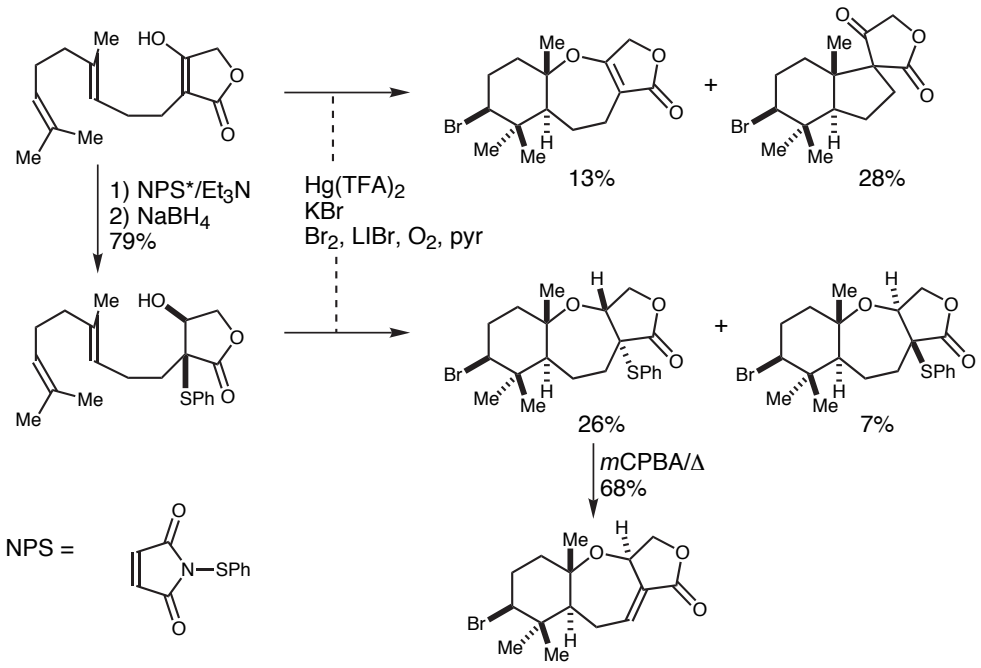



***(+/-)-Aplysistatin***

***12-epi-(+/-)-Aplysistatin***


Hoye, T. R., et al, *J. Am. Chem. Soc.*, **1979**, *101*, 5065-5067

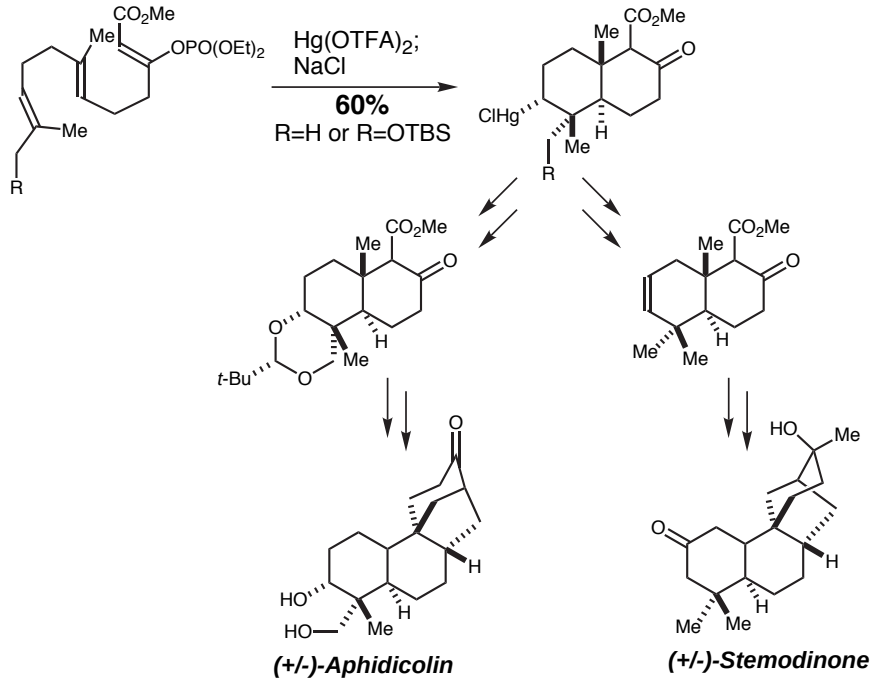
## *Synthesis of* Aplysia *Natural Products: White's Aplysistatin*




White, J. D., *J. Am. Chem. Soc.*, **1982**, *104*, 3923-3928

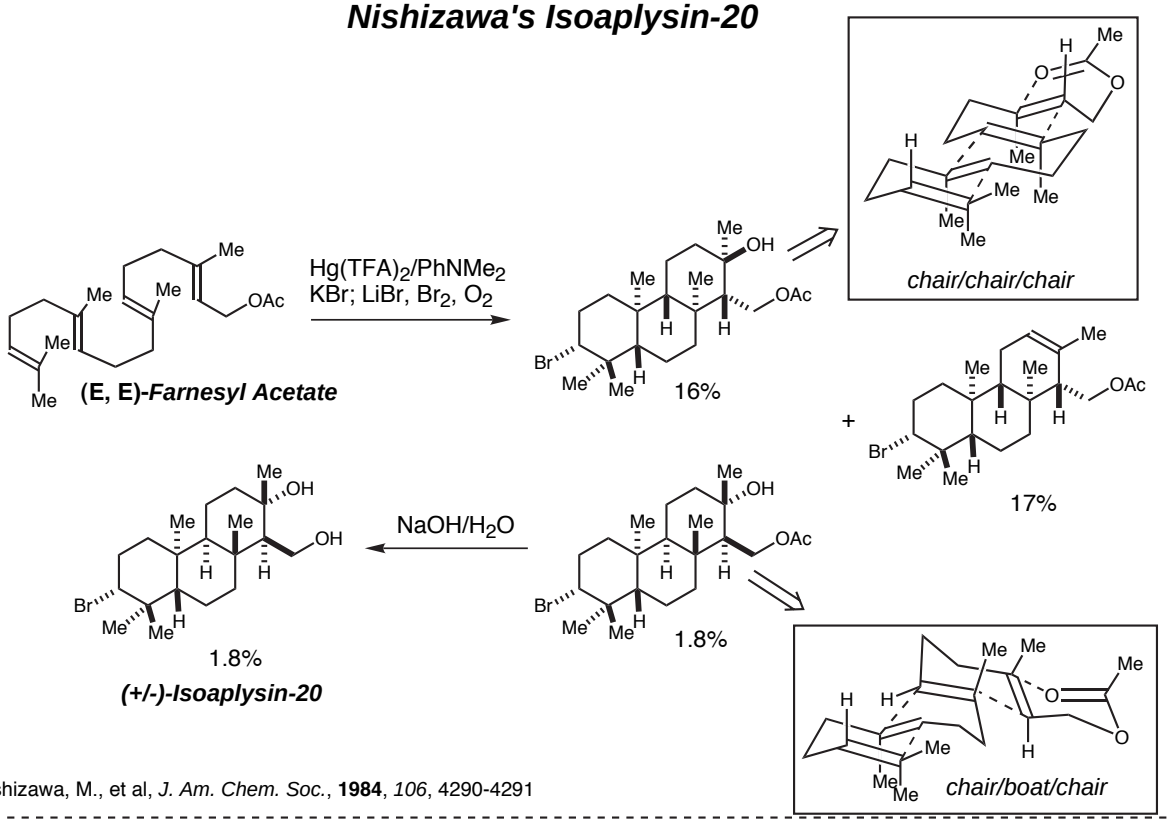
---

## *Corey's Use of Mercuriocyclization: Aphidicolin & Stemodinone*




Corey, E. J. et al, *J. Am. Chem. Soc.*, **1980**, *102*, 1742-1744
Corey, E. J. et al, *J. Am. Chem. Soc.*, **1980**, *102*, 7612-7613

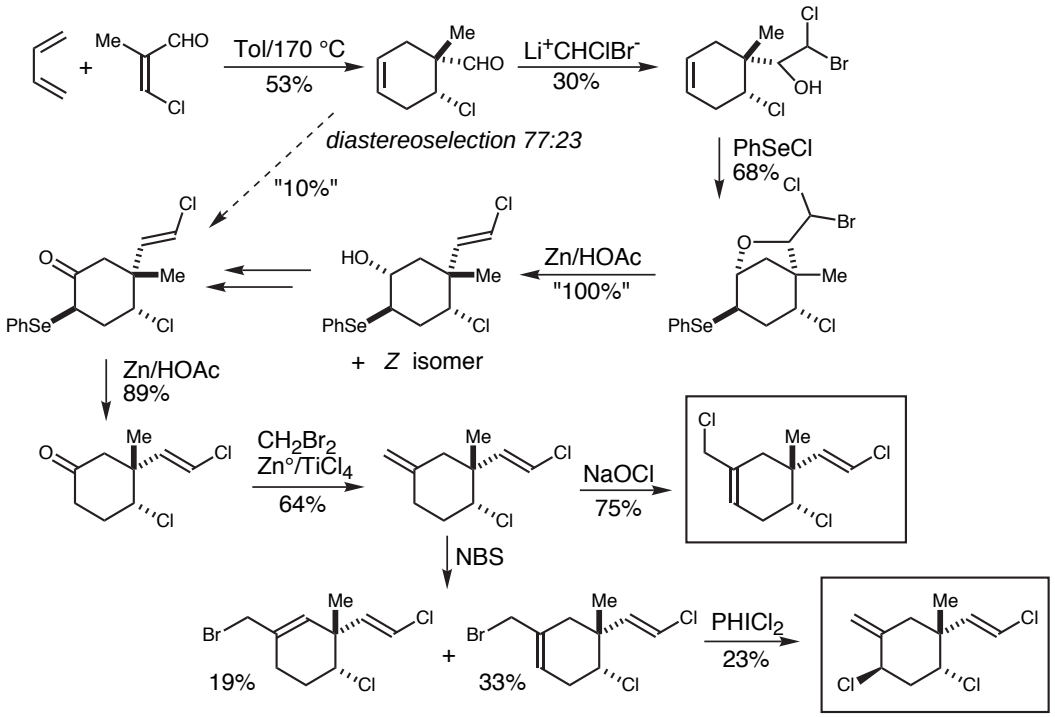
## *Synthesis of* Laurencia *Natural Products: Nishizawa's Isoaplysin-20*




Nishizawa, M., et al, *J. Am. Chem. Soc.*, **1984**, *106*, 4290-4291

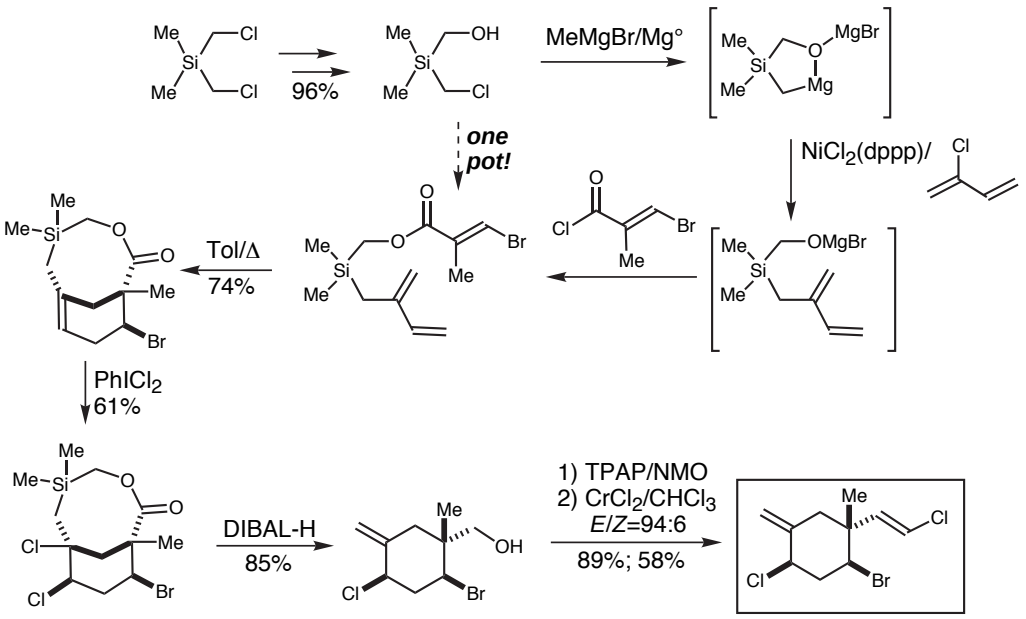
---

## *Synthesis of* Plocamium *Natural Products: The Diels-Alder approach*




Williard, P. G., et al, *J. Org. Chem.*, **1985**, *50*, 3738-3749.

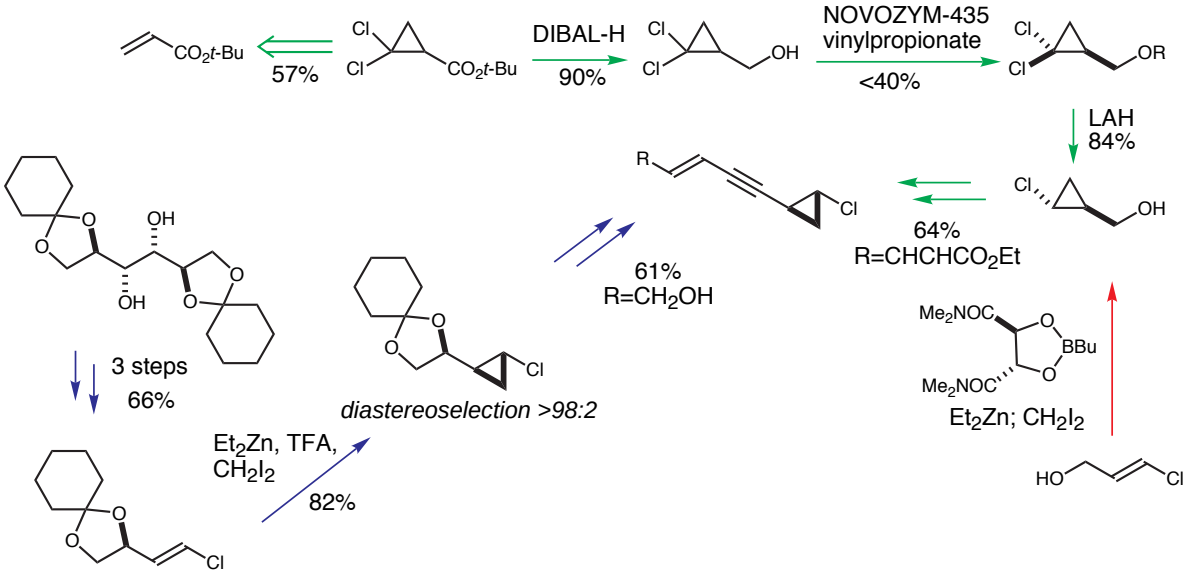
## *Synthesis of* Plocamium *Natural Products: Shea's T2IM Diels-Alder Approach*




Shea, K. J., et al, *J. Org. Chem.*, **1997**, *62*, 8962-8963

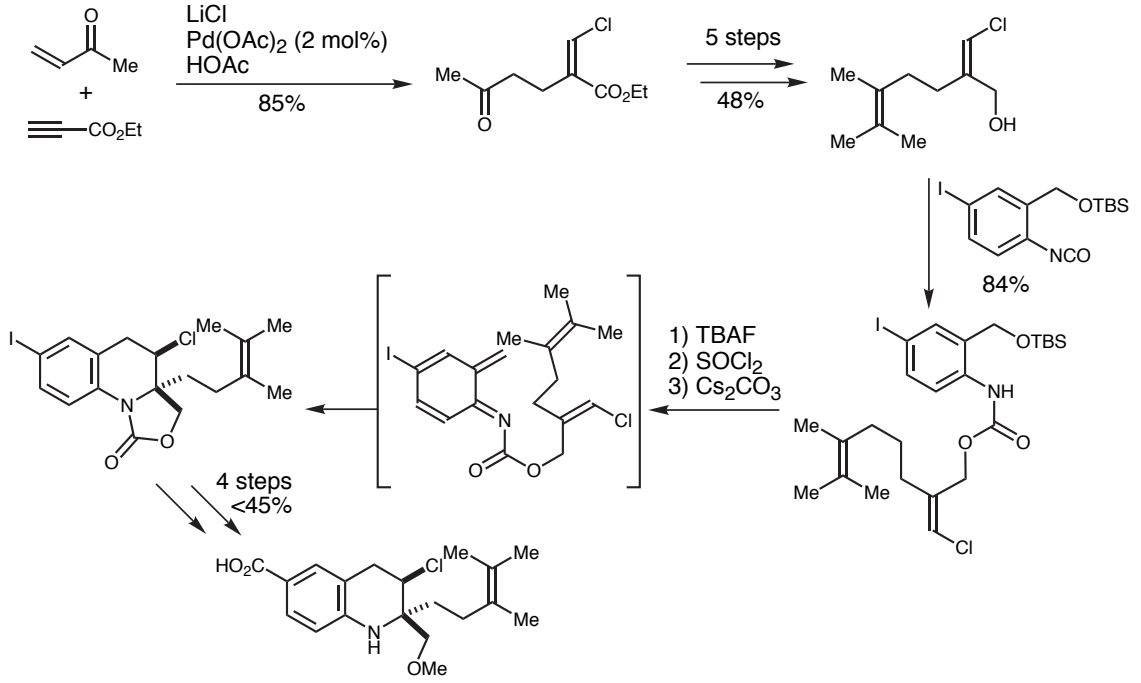
---

## *Synthesis of Callipeltoside Sidechain: Chloroalkene Cyclopropanation*




Olivo, H., et al, *Org. Lett.*, 2001, *2*, 4055-4058
Evans, D. A., et al, *Org. Lett.*, 2001, *3*, 503-505
Patterson, I., et al, *Angew. Chem. Int. Ed.*, 2001, 603-607

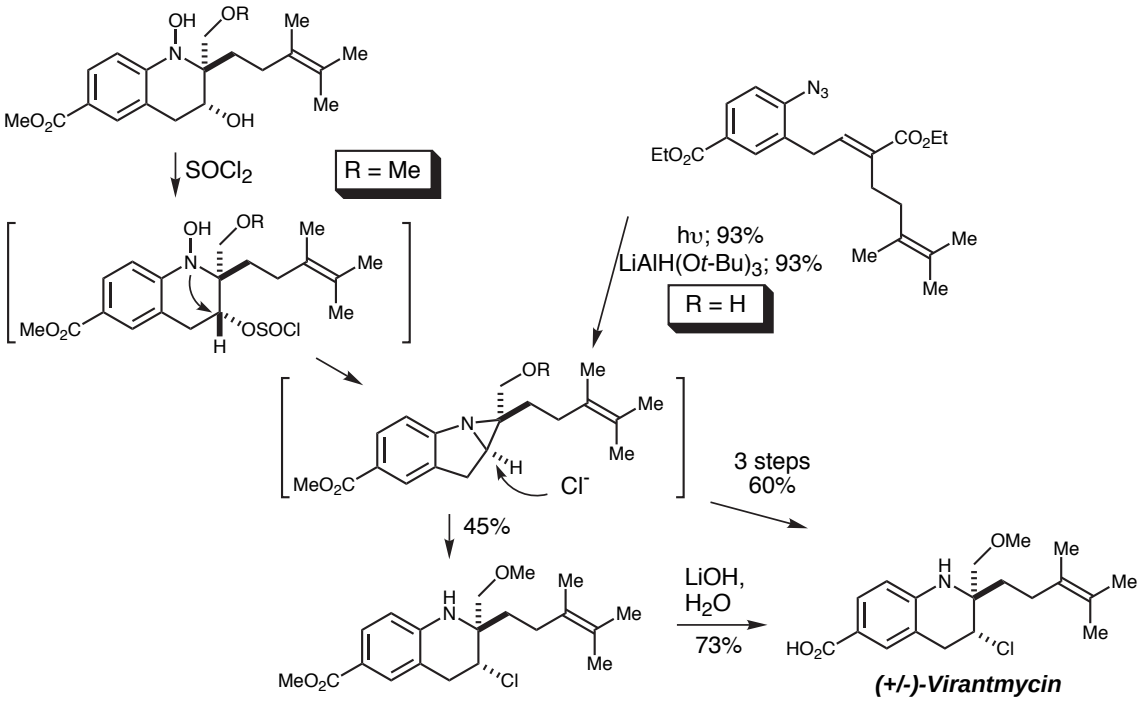
## *Synthesis of Virantmycin: Corey's Ortho-Azaxylylene Intramolecular Diels-Alder*




Corey, E. J., et al, *Org. Lett.*, **1999**, *1*, 824-825

---

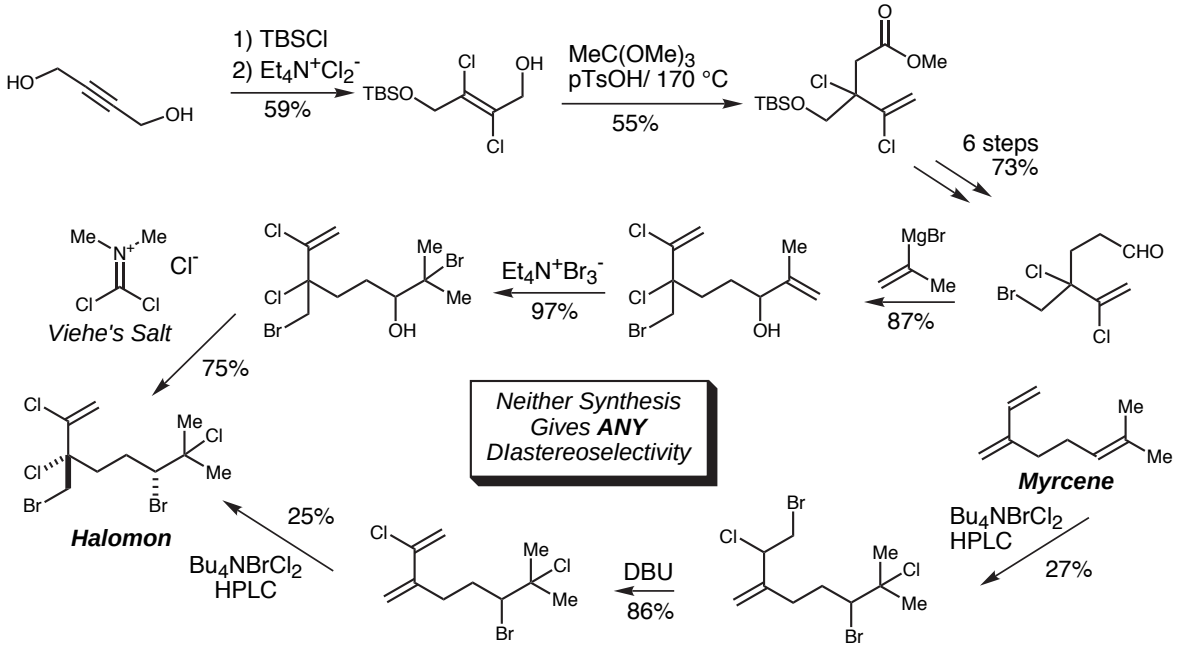
## *Synthesis of Virantmycin: Previous Syntheses by Raphael and Shirahama*




Shirahama, H., et al, *Synlett*, **1991**, 202-204
Raphael, R. A. , et al, *Tetrahedron*, **1990**, *46*, 4587-4594

## *Halomon: The Final Frontier*

- The biggest challenge in HNP synthesis is the preparation of acyclic halogenated terpenes
- Only two syntheses of Halomon have been reported, and there is still much room for improvement

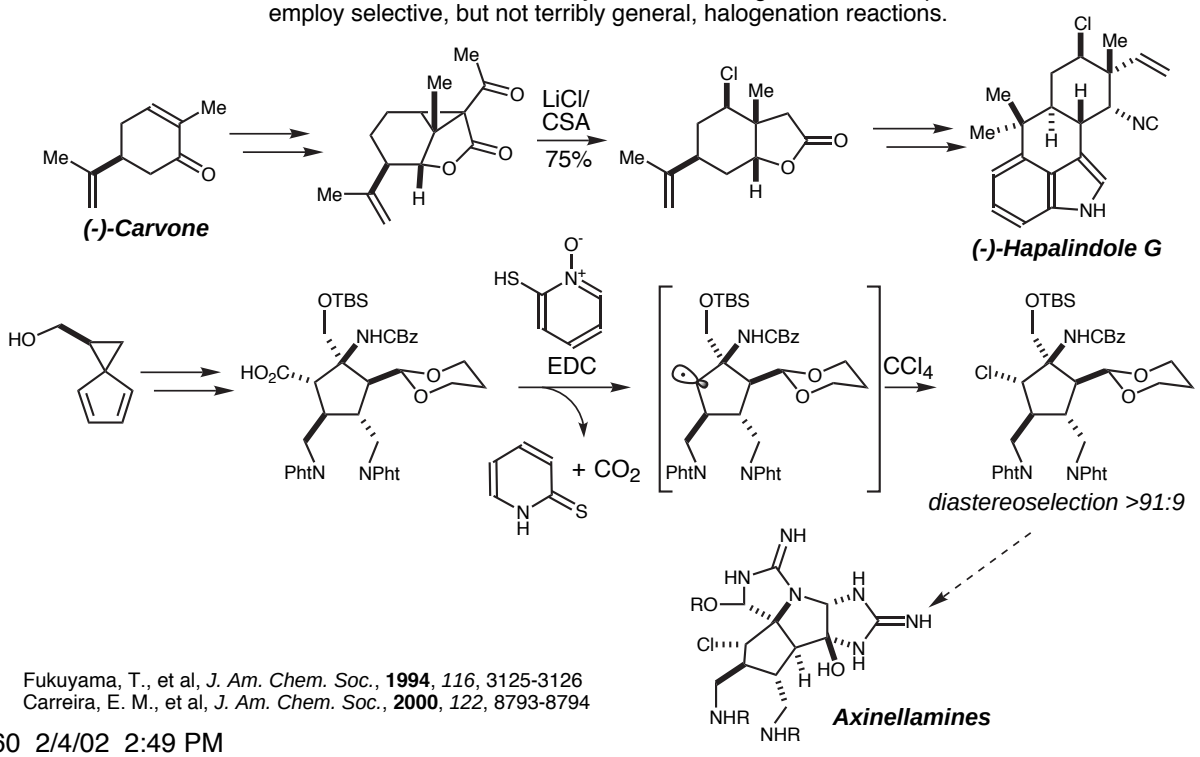



Mioskowski, C., et al, *Angew. Chem. Int. Ed.*, **1998**, *37*, 2085-2086
Hirama, M., et al, *Angew. Chem. Int. Ed.*, **2000**, *39*, 3430-3431

---

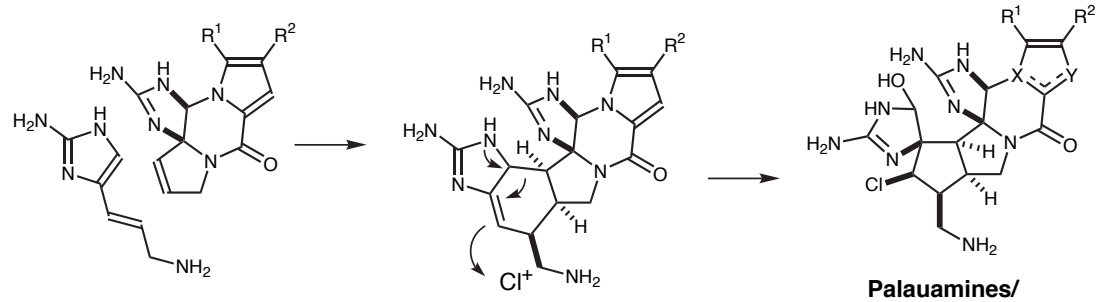
## *Outlyers*

- Several recent diastereoselective syntheses of halogenated natural products employ selective, but not terribly general, halogenation reactions.

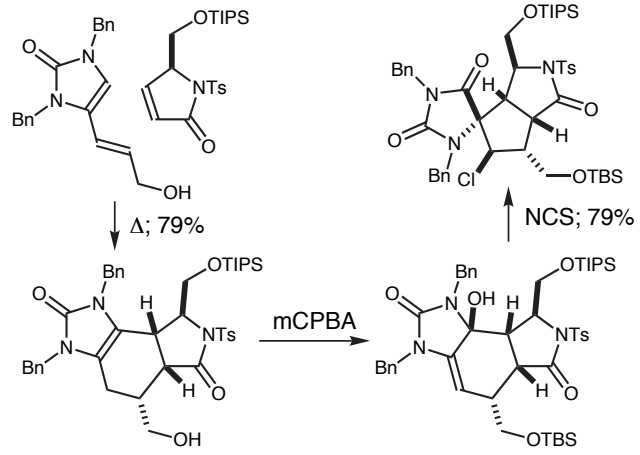



Fukuyama, T., et al, *J. Am. Chem. Soc.*, **1994**, *116*, 3125-3126
Carreira, E. M., et al, *J. Am. Chem. Soc.*, **2000**, *122*, 8793-8794

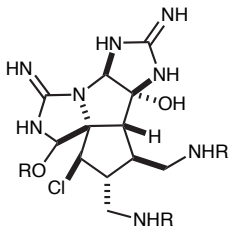
## *Outlyers II*



**Palauamines/ Styloguanidines**




***diastereoselection 81:19***



***Axinellamines***


Kinnel, R. G., et al, *J. Am. Chem. Soc.*, **1993**, *115*, 3376-3377
Romo, D., et al, *Org. Lett.*, **2001**, *3*, 1535-1538
Poitier, P., et al, *Eur. J. Org. Chem.*, **2001**, 237-243


## *Summary*

- Many selective approaches to the construction of halogen-bearing stereocenters have been developed
- Nucleophilic displacement of alcohols is an important and selective method for the construction of a bromine-bearing center
- Mono- and polycyclizations provide the opportunity to use the introduction of bromine to control the stereo- and regiochemistry of other stereogenic centers
- Few methods are truly general and most are developed in the context of one particular natural product class