

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

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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.

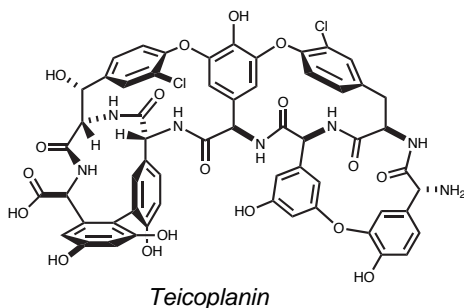
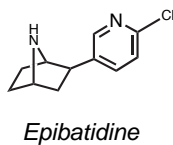
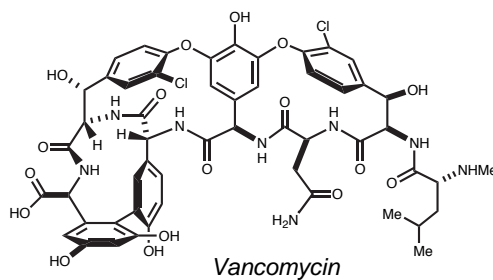
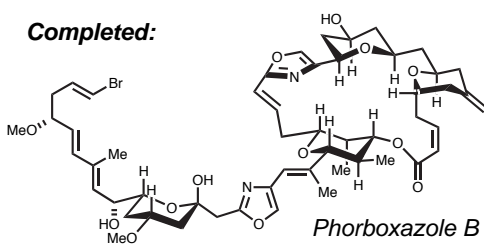
Franssen, M. C. R., *Catalysis Today*, **1995**, 22, 441-457.

Synthesis of Halogenated Natural Products:

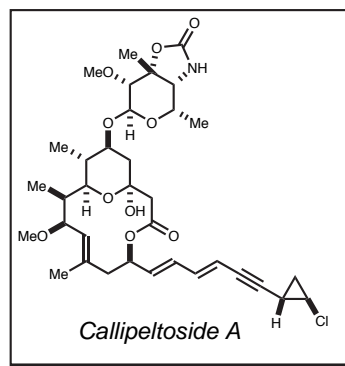
Murai, A., *Studies in Natural Products Chemistry*, **1997**, 19, 411-461.

Halogenated Natural Products Synthesized in the Evans Group

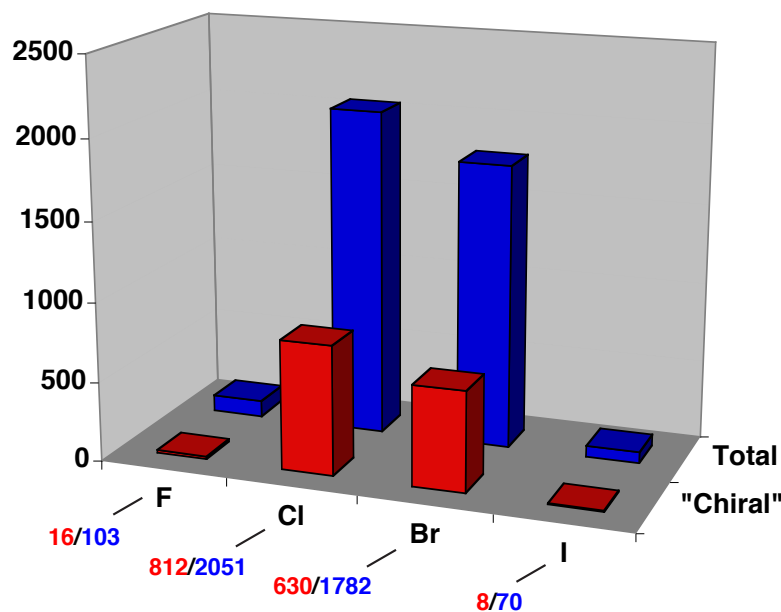
Completed:



In Progress:



Distribution of Halogenated Natural Products



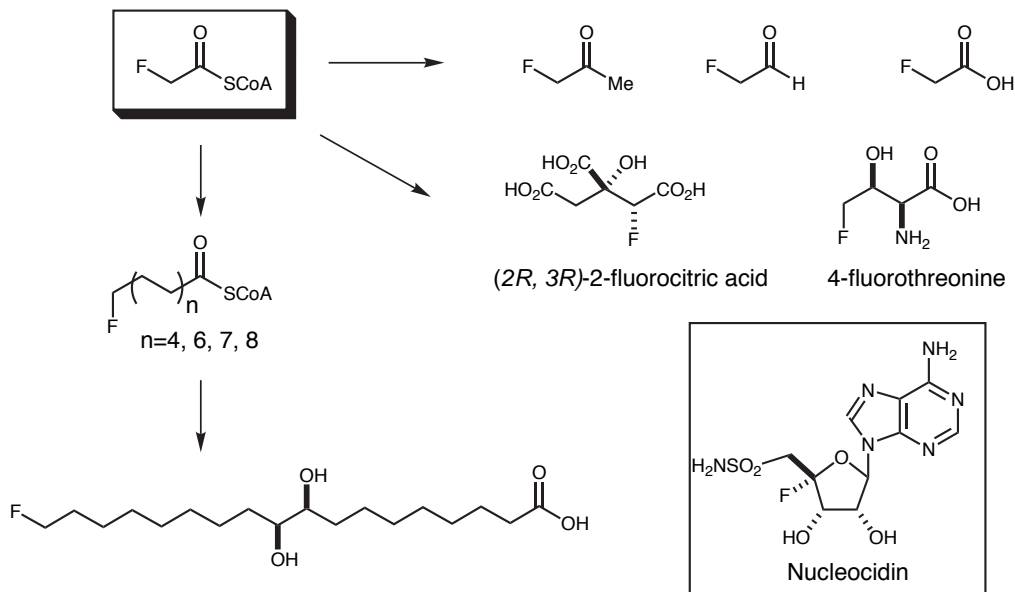
"Chiral" = Contains A Halogen-Bearing Stereocenter

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. Oppositol, prepinnaterpene, laurencial, dactylyne
 2. Comparative syntheses of laurencin and related structures
 3. Comparative syntheses of kumausyne and kumausallene
 4. Syntheses aphysiapyranoids and thyriferol/venusatriol by electrophilic monocyclization
 5. Selected polycyclizations leading to natural products
 6. Diels-Alder approaches to plocamium natural products and virantmycin
 7. Callipeltoside sidechain
 8. Halomon
 9. Outlyers: Hapalindole G & Axinellamines

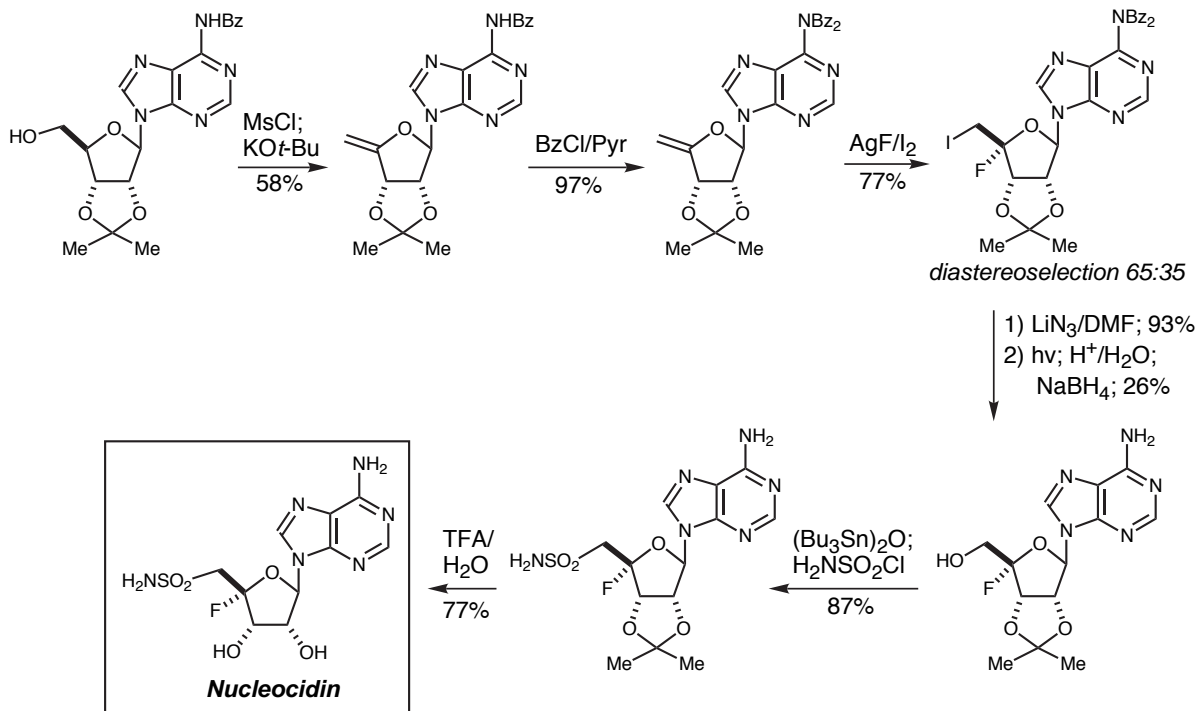
The Fluorinated Natural Products

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



Gribble, 1996

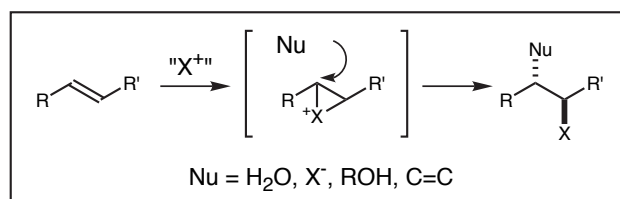
The Fluorinated Natural Products: Moffatt's Synthesis of Nucleocidin



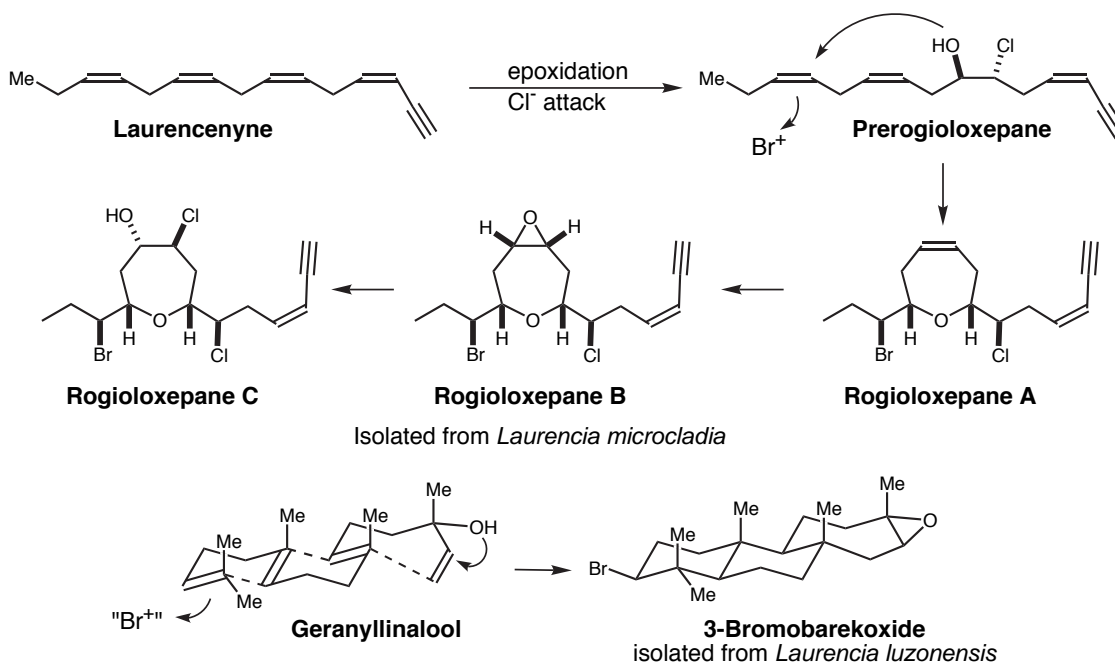
The Biogenic Origin of Halogenated Natural Products

- Chlorine is incorporated by nucleophilic displacement as Cl^- or through the reactions of alkenes with chloroperoxidases (CPO's), ie as " Cl^+ "
- Bromine is almost exclusively incorporated 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!

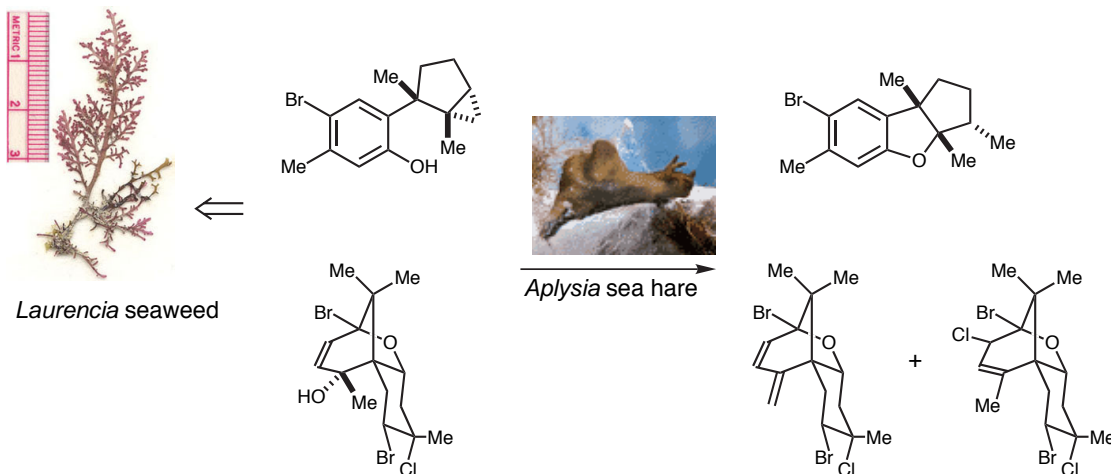


Examples of Halogen Biosynthesis



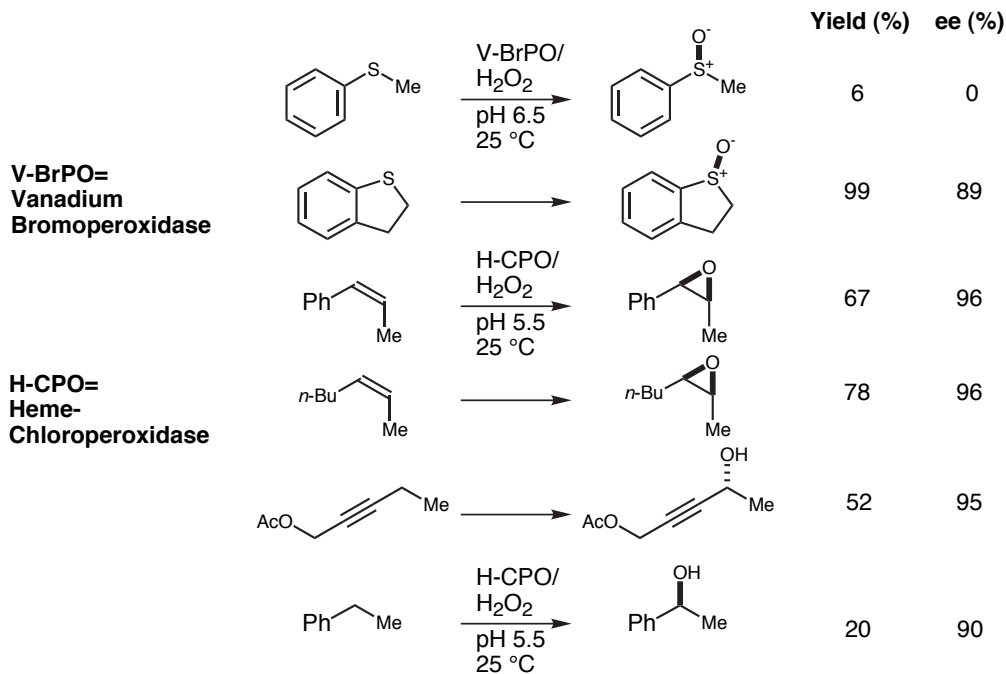
Examples of Halogen Biosynthesis

- 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



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

Haloperoxidases Catalyze Selective Oxidations



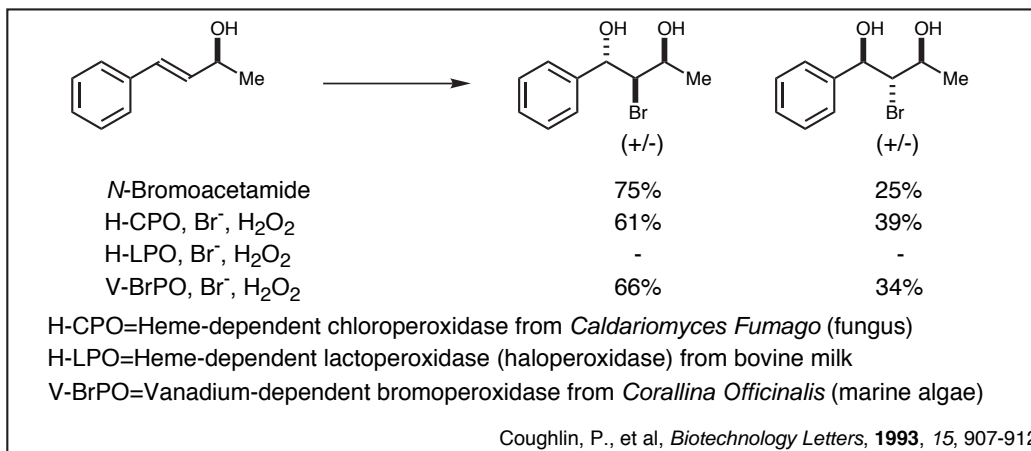
Sulfoxidation: Allenmark, A., et al, *J. Org. Chem.*, **1997**, *62*, 8455-8458

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

Benzilyc Oxidation: Zaks, A., et al, *J. Am. Chem. Soc.*, **1995**, *117*, 10419-10424

Haloperoxidases Catalyze Unselective Bromohydrin Formation

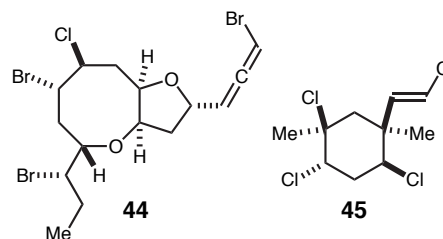


"One of the most interesting, yet unsolved problems in the area of marine biohalogenation, is the biogenesis of the chiral halogenated marine natural products."

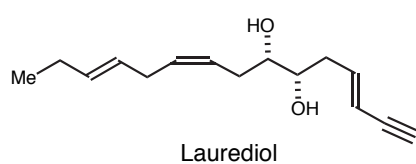
Butler, A. *Chem. Rev.*, **1993**, 93, 1937-1944.

"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**."

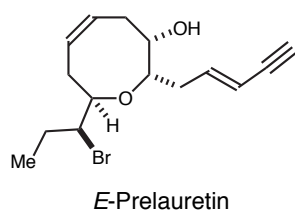
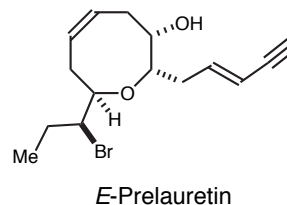
Franssen, M. C. R., *Catalysis Today*, **1994**, 22, 441-457



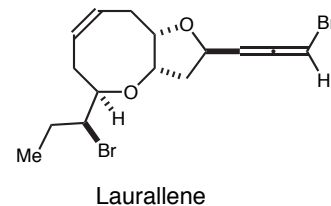
Enzyme-Catalyzed Bromohydrin Formation



Lactoperoxidase;
NaBr, H₂O₂, pH 5.5
0.05% Yield
(0.41% BORSM)



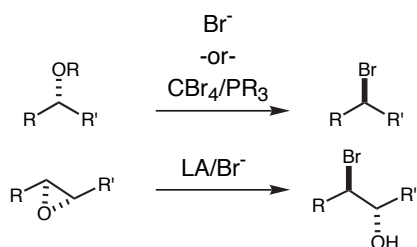
Lactoperoxidase;
NaBr, H₂O₂, pH 5.5
0.03% Yield
(0.19% BORSM)



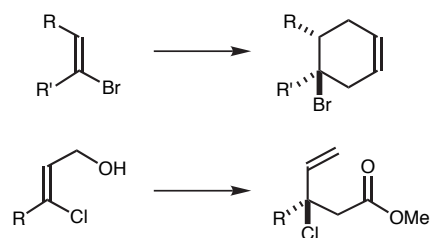
Murai, A., et al:
Tetrahedron Lett., **1995**, 36, 737-740
Tetrahedron, **1997**, 53, 8371

Methods of Halogenation

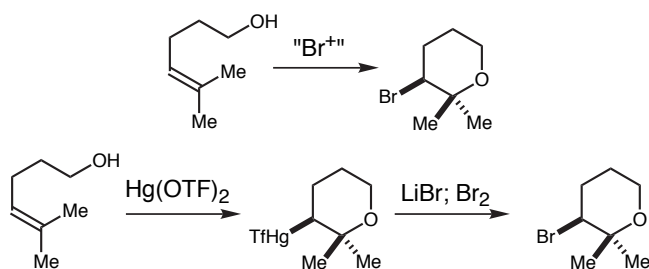
Nucleophilic Displacement:



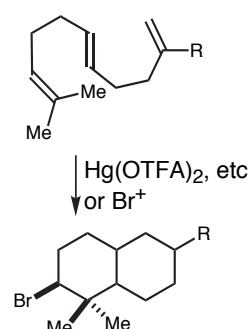
Cycloaddition/Sigmatropic Rearrangement:



Bromoetherification/ Oxymercuration-Bromination

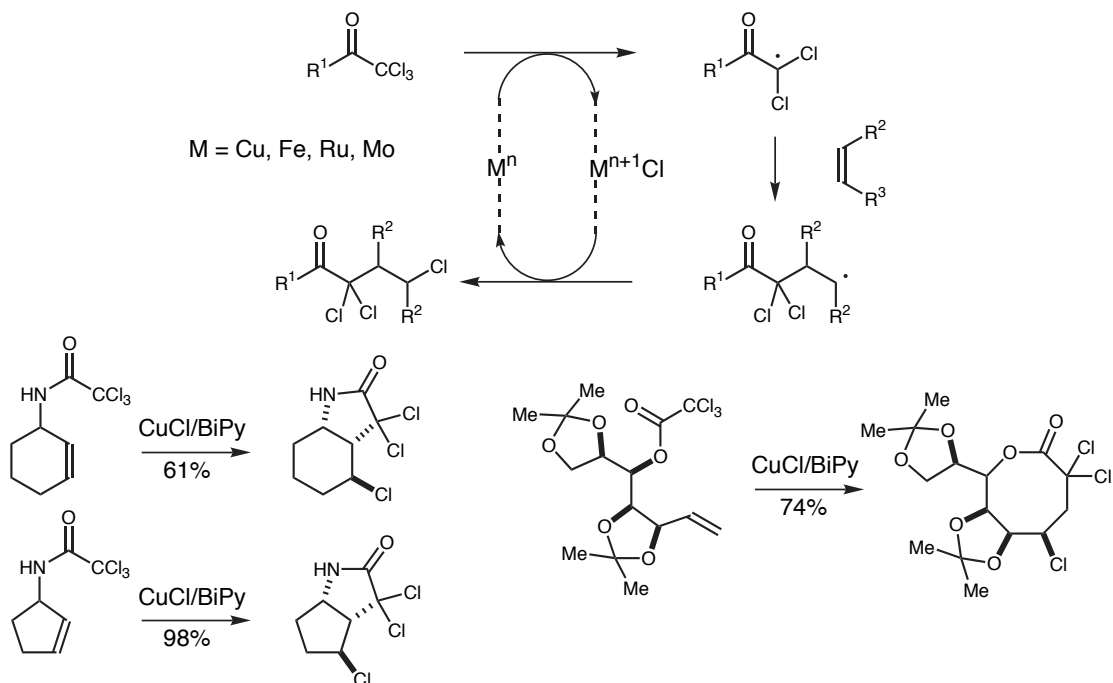


Polyene Cyclization



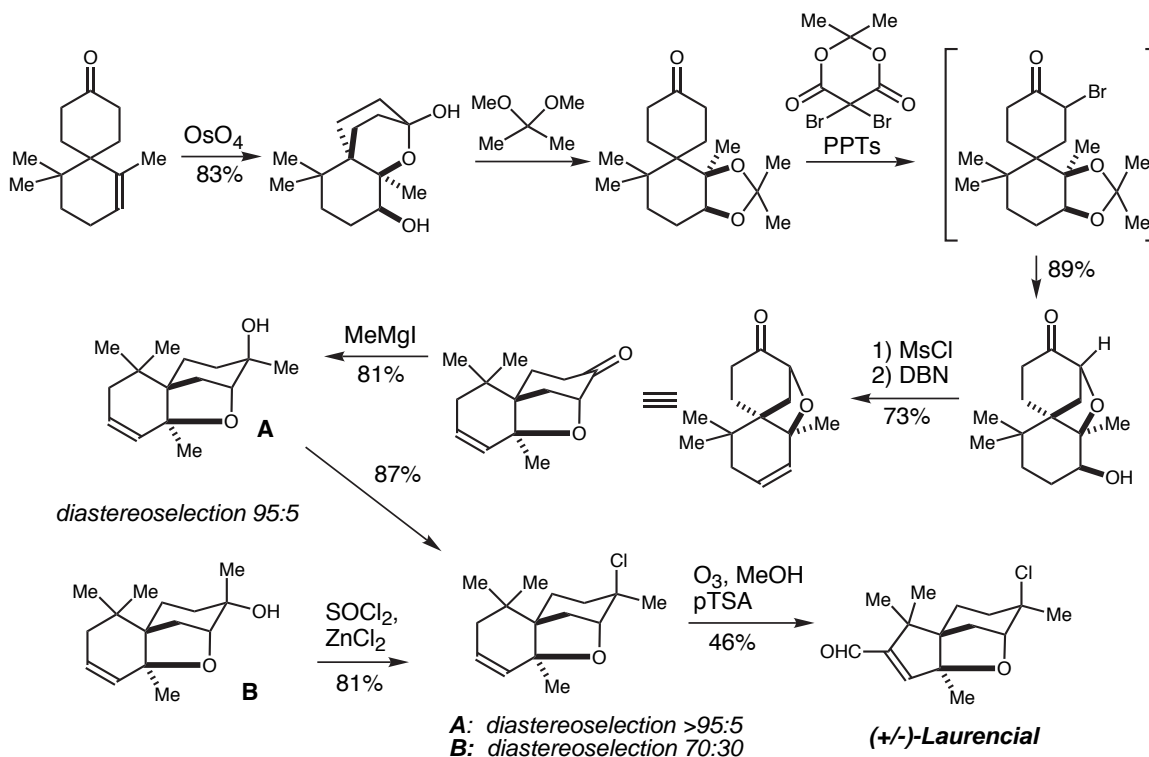
Methods of Halogenation

The Kharasch Reaction:



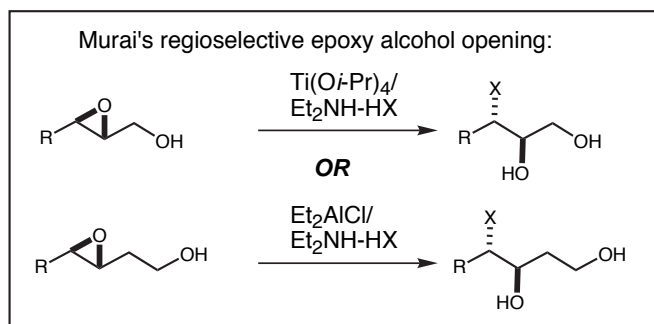
Weinreb, S. M., et al, *Tetrahedron*, **1988**, *44*, 4671-4678
 Itoh, K., et al, *J. Org. Chem.*, **1993**, *58*, 464-470
 Speckamp, W. N., et al, *Synlett*, **1993**, 739

Synthesis of Laurencia Natural Products: Iwata's Laurencial

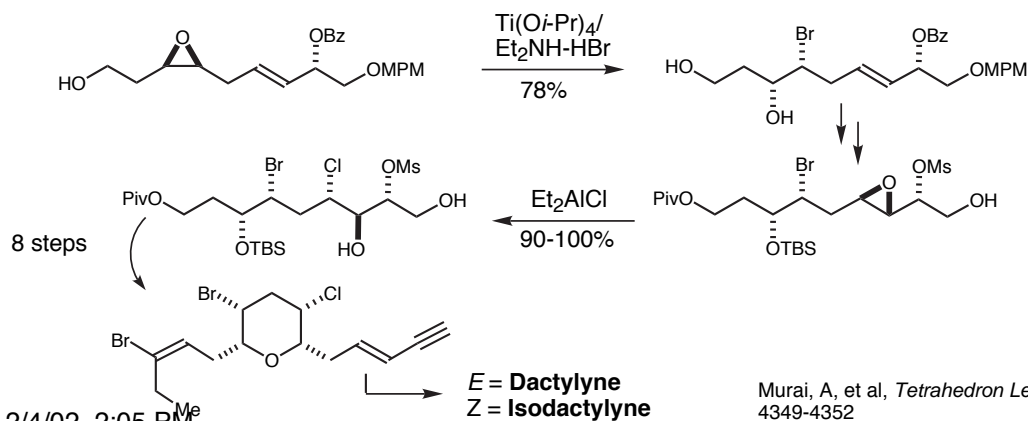


Iwata, C, et al, *Tetrahedron*, **1998**, 54, 1396-1406

Synthesis of Dactylyne



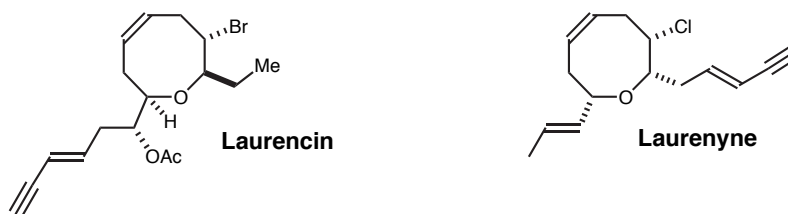
see also Sharpless, K. B., et al, *J. Org. Chem.*, **1985**, 50, 1557-1560



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

Synthesis of Laurencia Natural Products

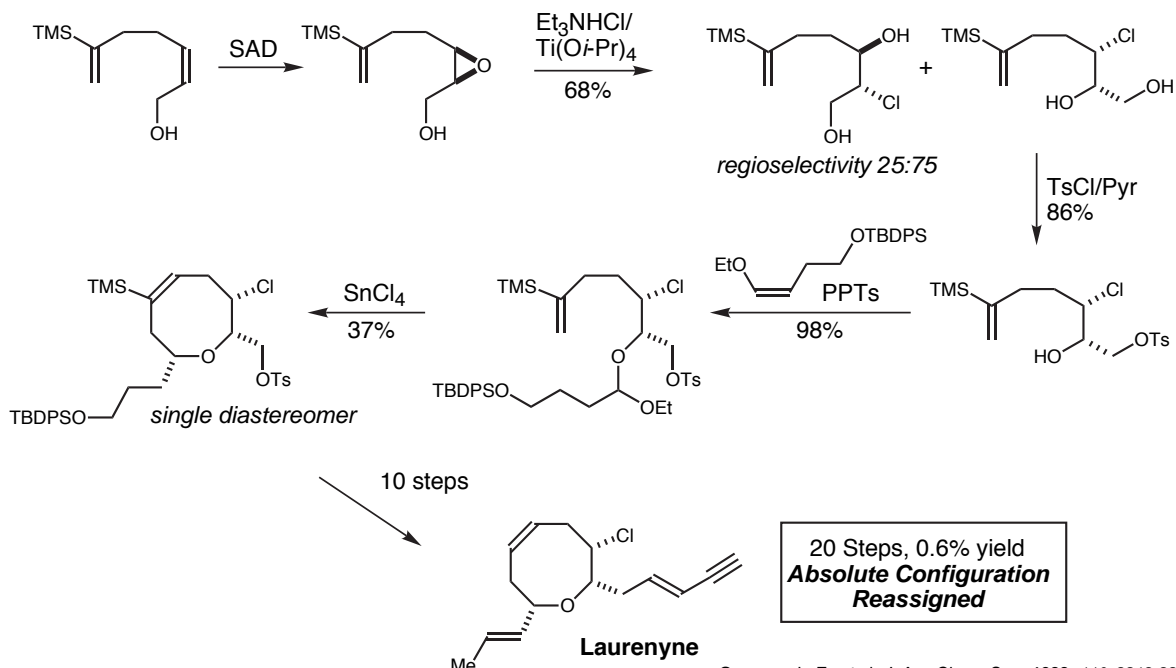
- Before the 1988 synthesis of Laurenyne by Overman, there was only one synthesis of an oxocane-containing natural product known, ie T. Masumune's synthesis of Laurencin in 0.003% yield.
- In the last decade, however, many syntheses of medium-ring ether natural products from the *Laurencia* series have appeared.



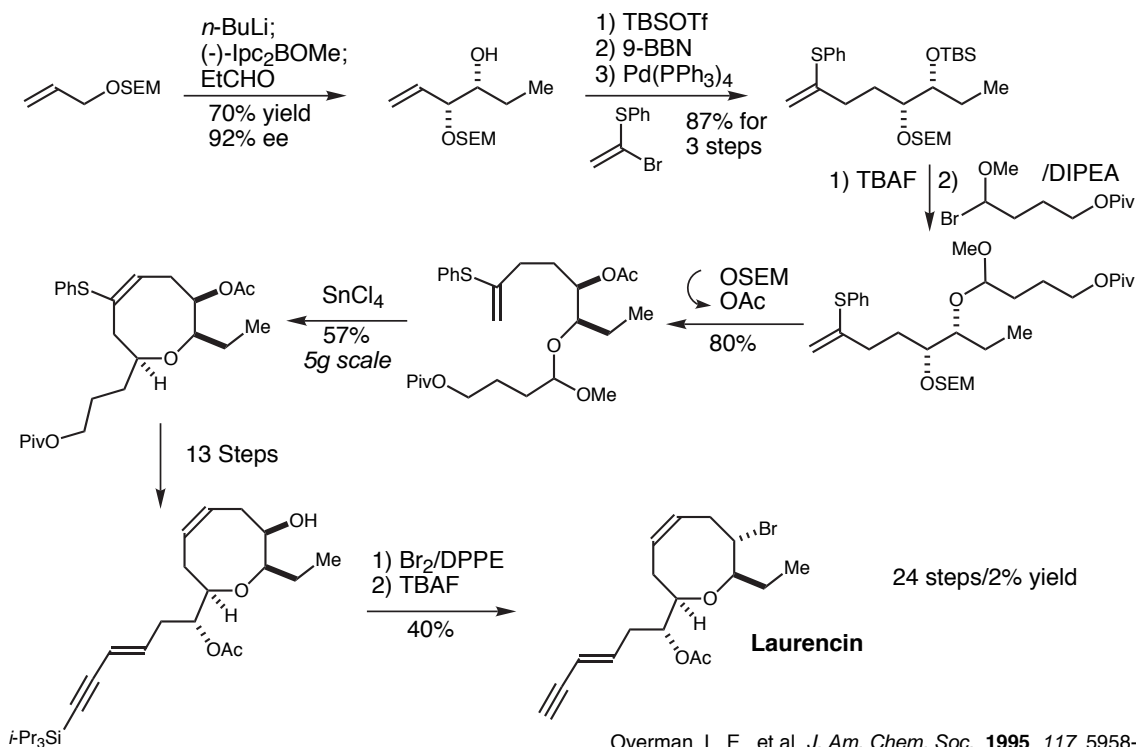
Principle Synthetic Challenges:

- 1) medium ring formation
- 2) diastereoselectivity across ring
- 3) regiochemical control of unsaturation

Overman's Synthesis of Laurencia Natural Products: Laurenyne

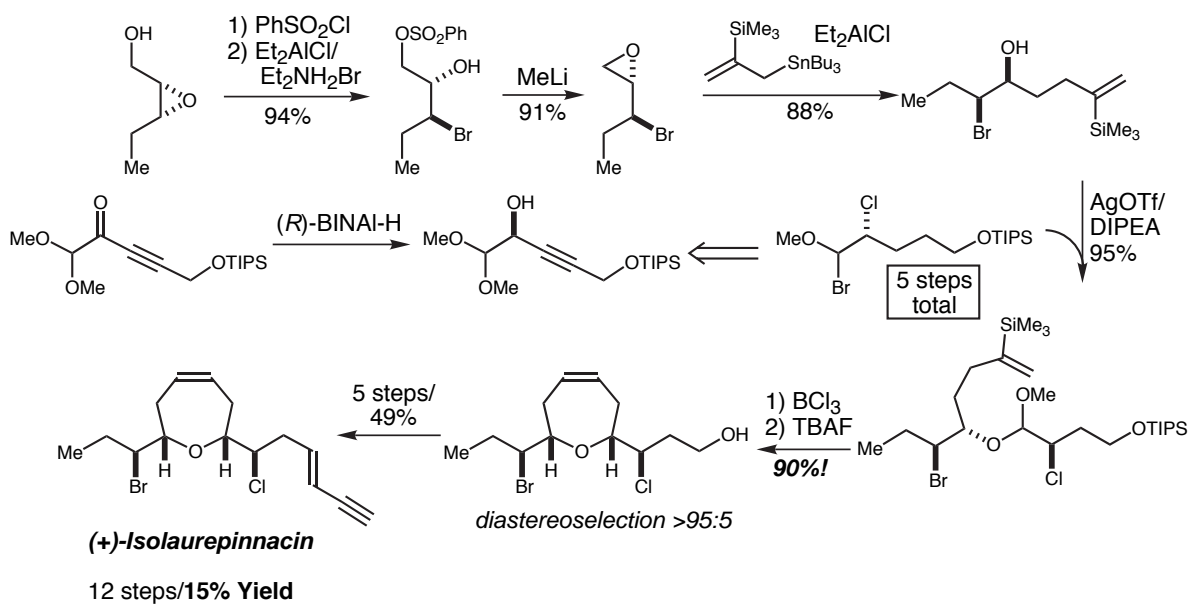


Overman's Synthesis of Laurencia Natural Products: Laurencin



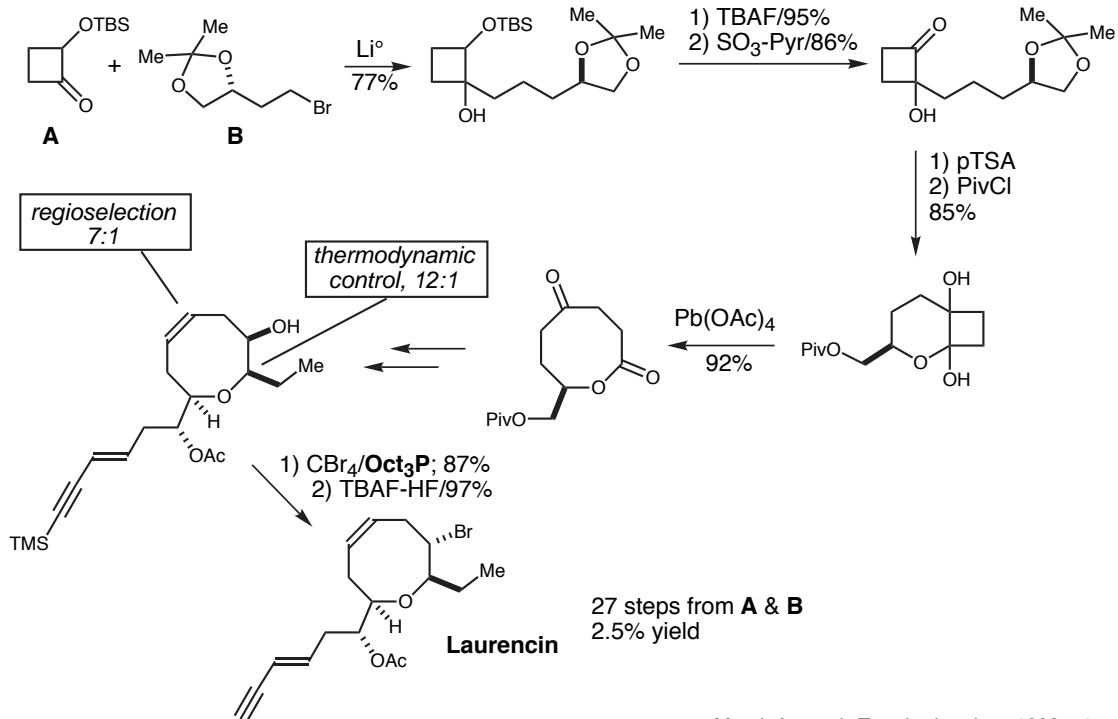
Overman, L. E., et al, *J. Am. Chem. Soc.*, **1995**, 117, 5958-5966

Overman's Synthesis of Laurencia Natural Products: Isolaurepinnacin



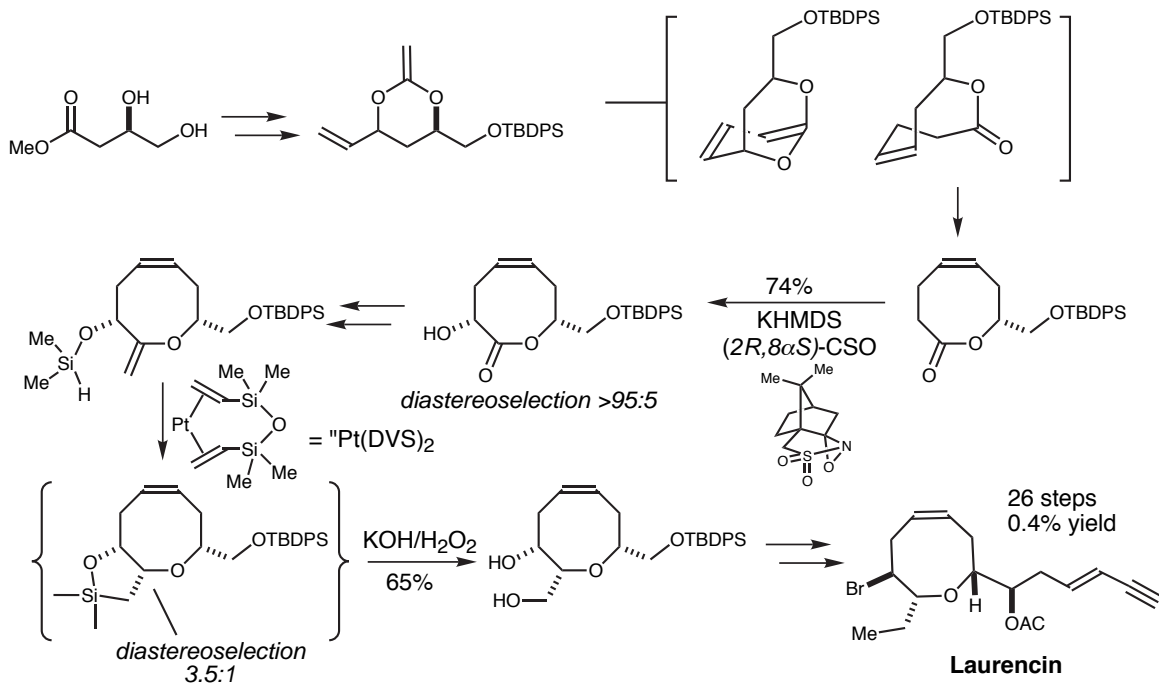
Overman, L. E., et al, *J. Am. Chem. Soc.*, **1993**, 115, 9305-9306

Murai's Synthesis of Laurencia Natural Products: Laurencin



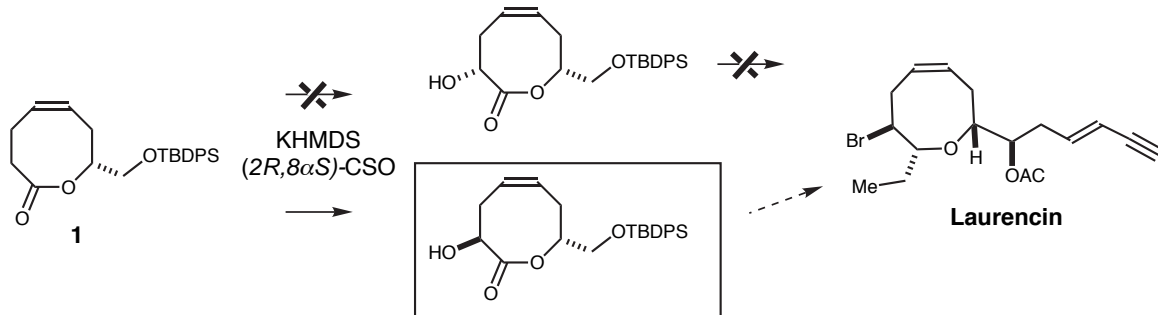
Murai, A., et al, *Tetrahedron Lett*, **1992**, 4345-4348

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



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

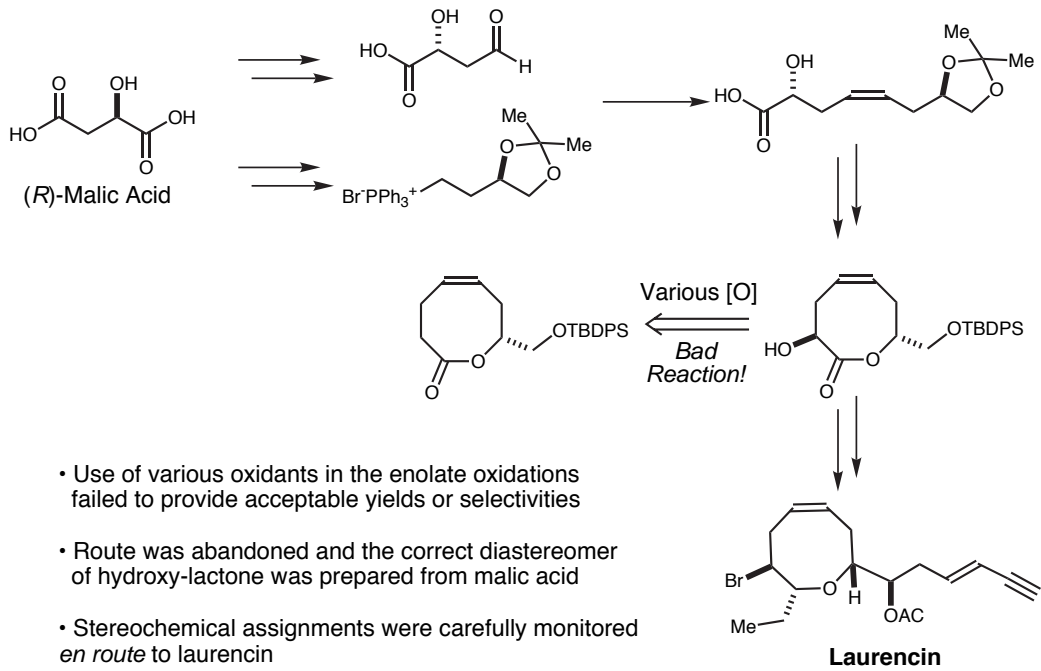
Synthesis of Laurencia Natural Products: Holmes & Clark's Laurencin - Retraction!



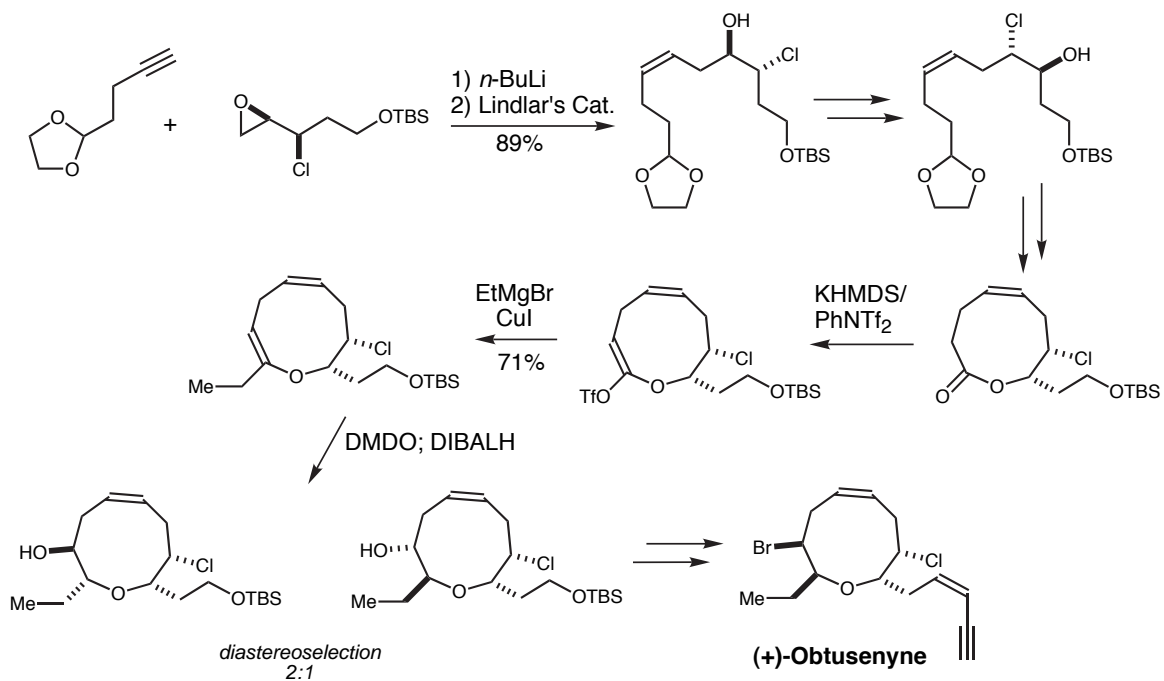
"The synthesis of lactone **1** as reported by J. S. Clark, Ph. D. Thesis, Cambridge University, 1988, is correct. The synthesis of (+)-laurencin in ref 1 is difficult to account for and must probably be charged to the fallibility of the other junior author and the gullibility of the senior author."

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

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

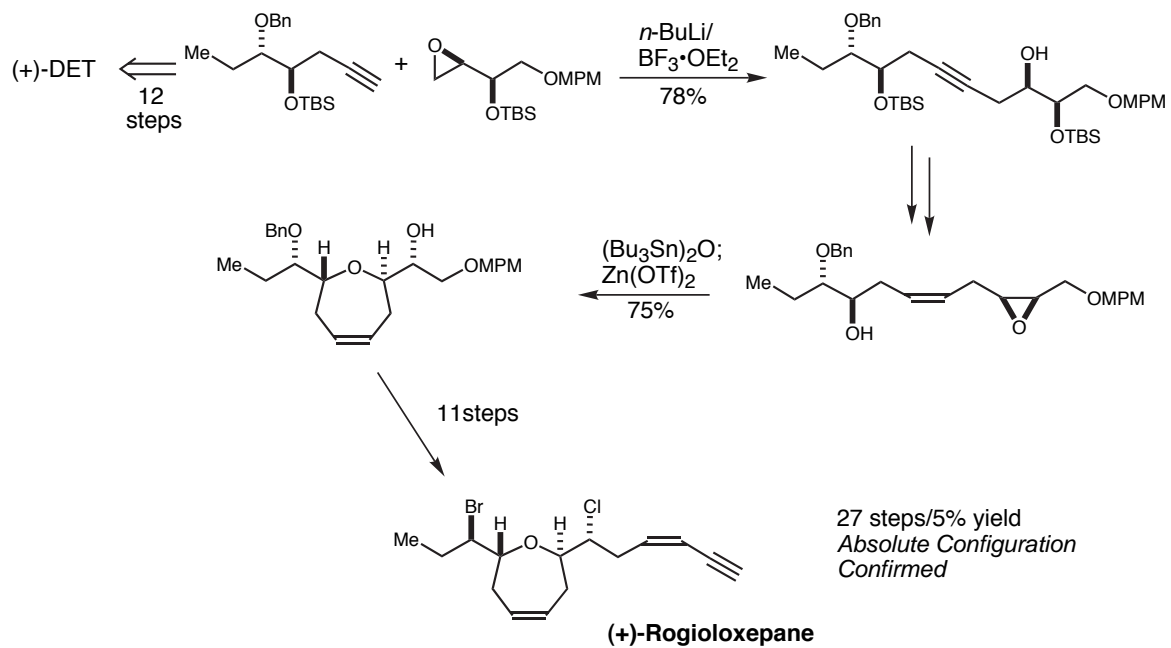


**Synthesis of Laurencia Natural Products:
Murai's Obtusenyne**

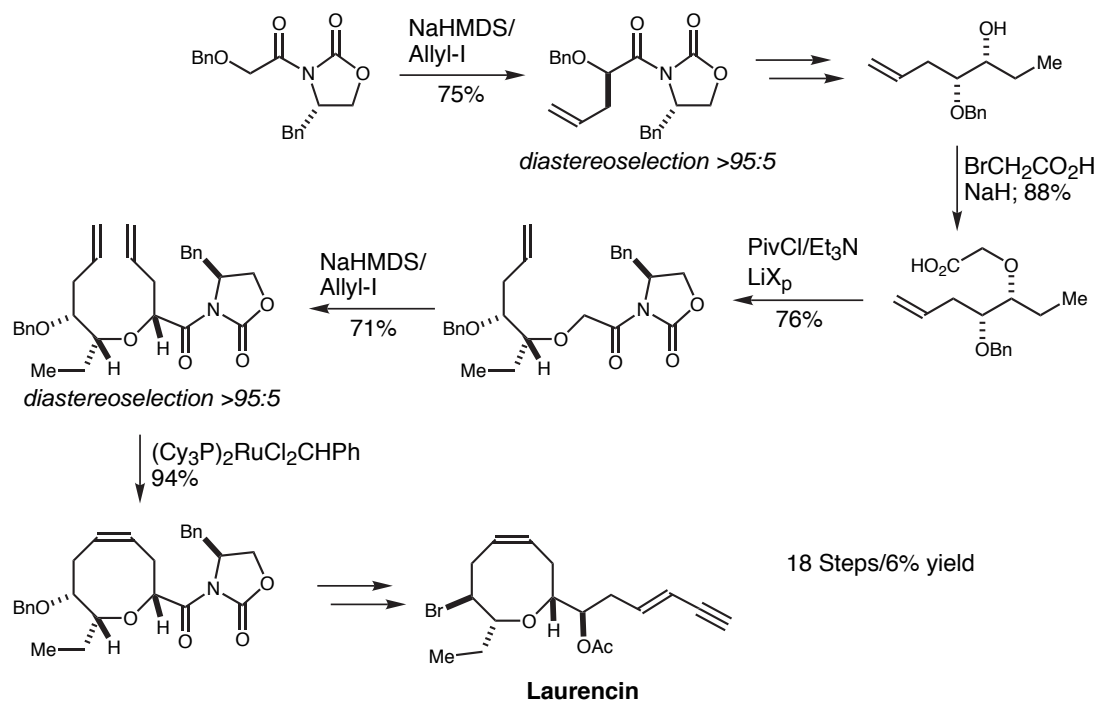


Murai, A., et al, *J. Org. Chem.*, **1999**, *64*, 2616-2617

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

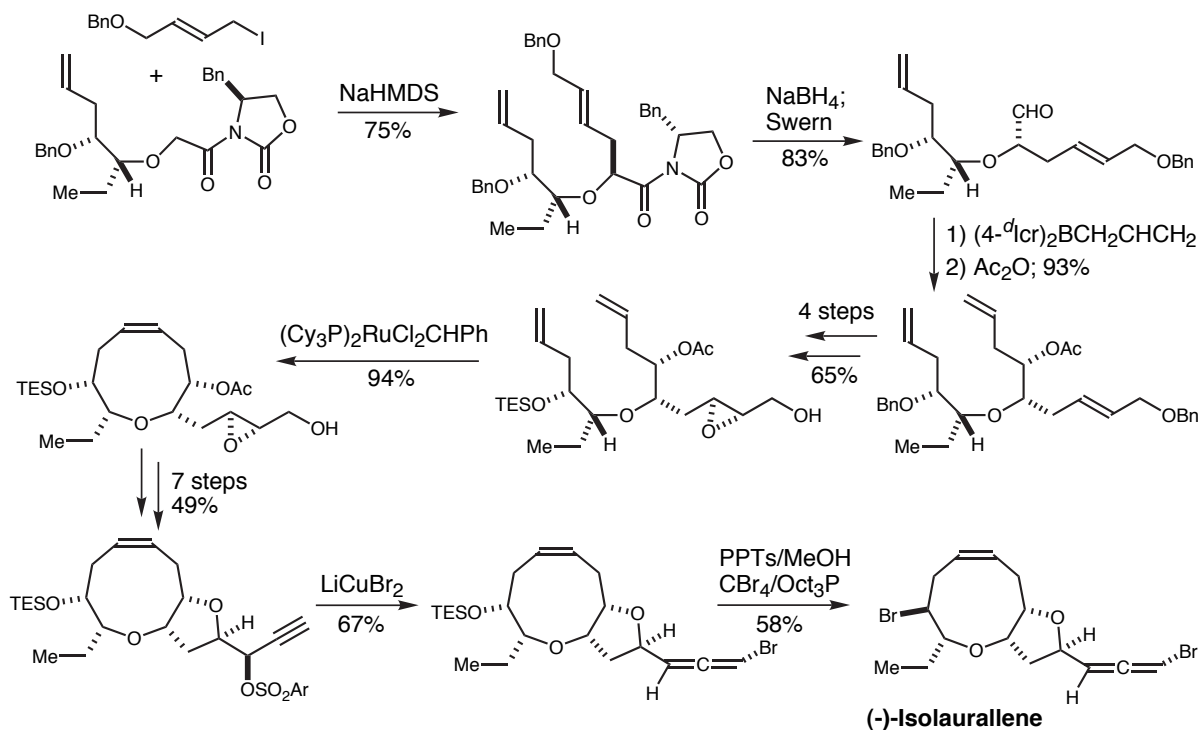


**Synthesis of Laurencia Natural Products:
Crimmins' Laurencin**



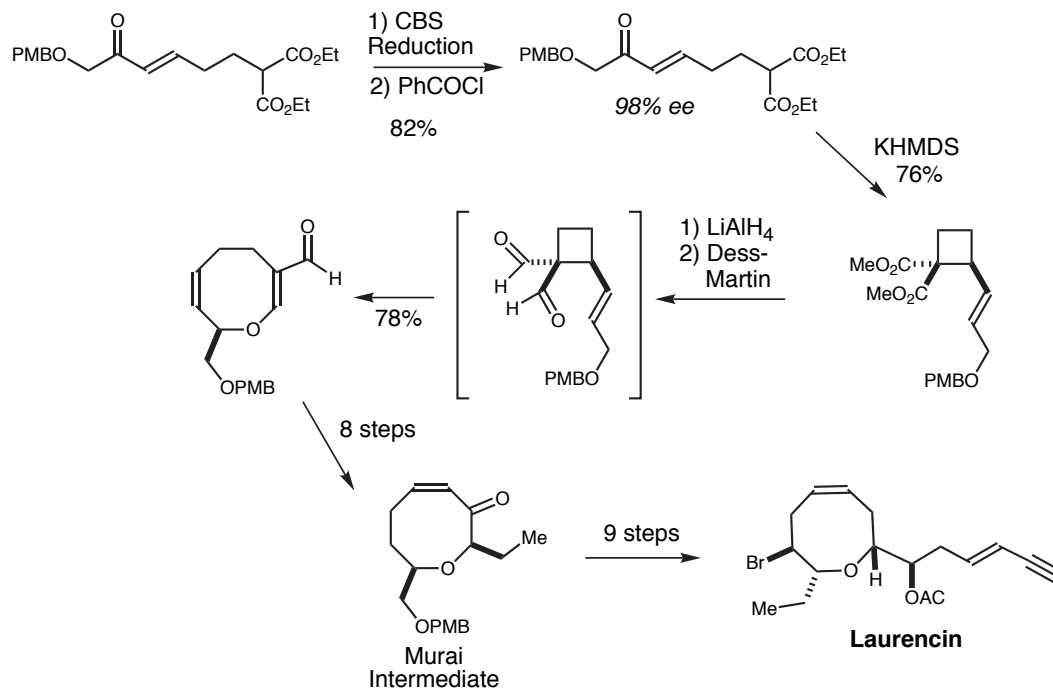
Crimmins, M. T., et al, *Org. Lett.*, **1999**, 1, 2029-2032

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



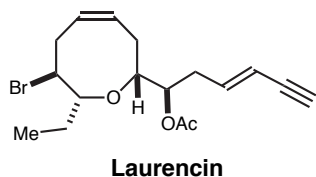
Crimmins, M. T., et al, *J. Am. Chem. Soc.*, **2001**, 123, 1533-1534

Boeckman's Laurencin



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

Synthesis of Laurencia Natural Products: Summary



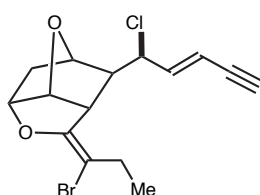
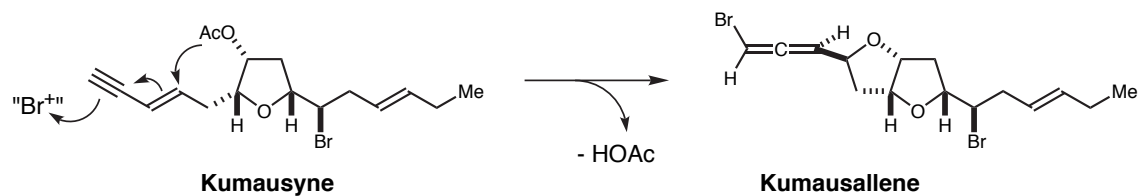
Principle Synthetic Challenges:

- 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

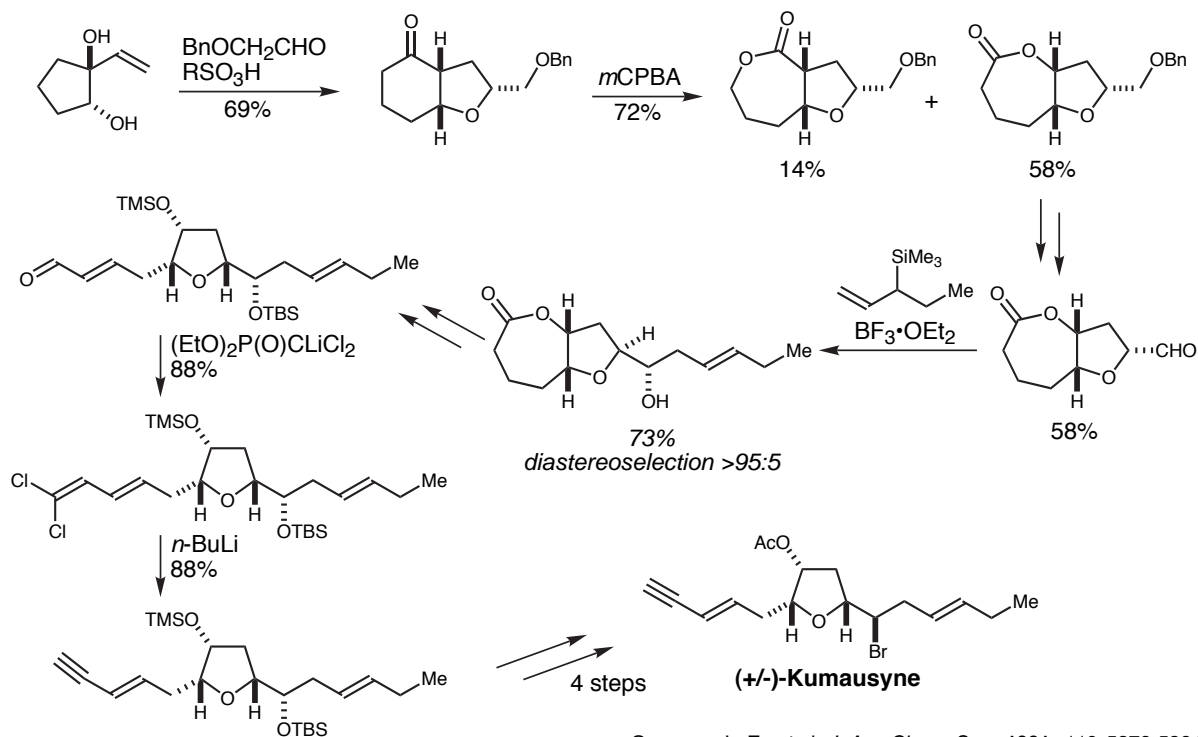
Synthesis of Laurencia Natural Products: Kumausyne & Kumausallene



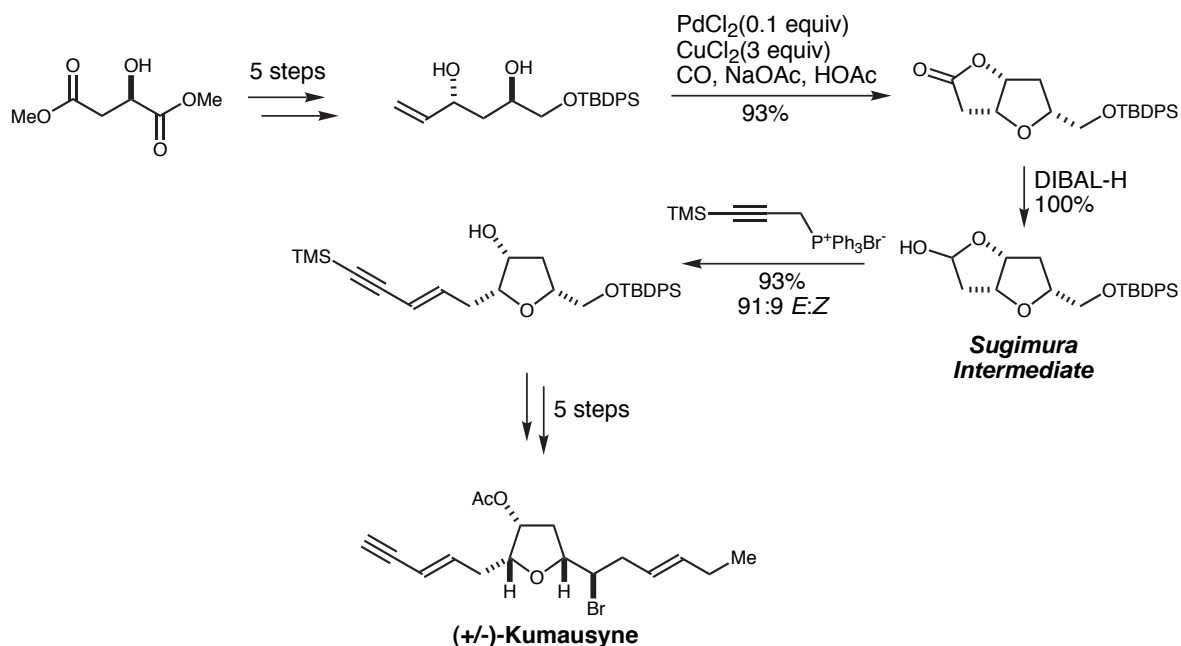
(+/-)-trans-maneonene-B

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

Synthesis of Laurencia Natural Products: Overman's Kumausyne

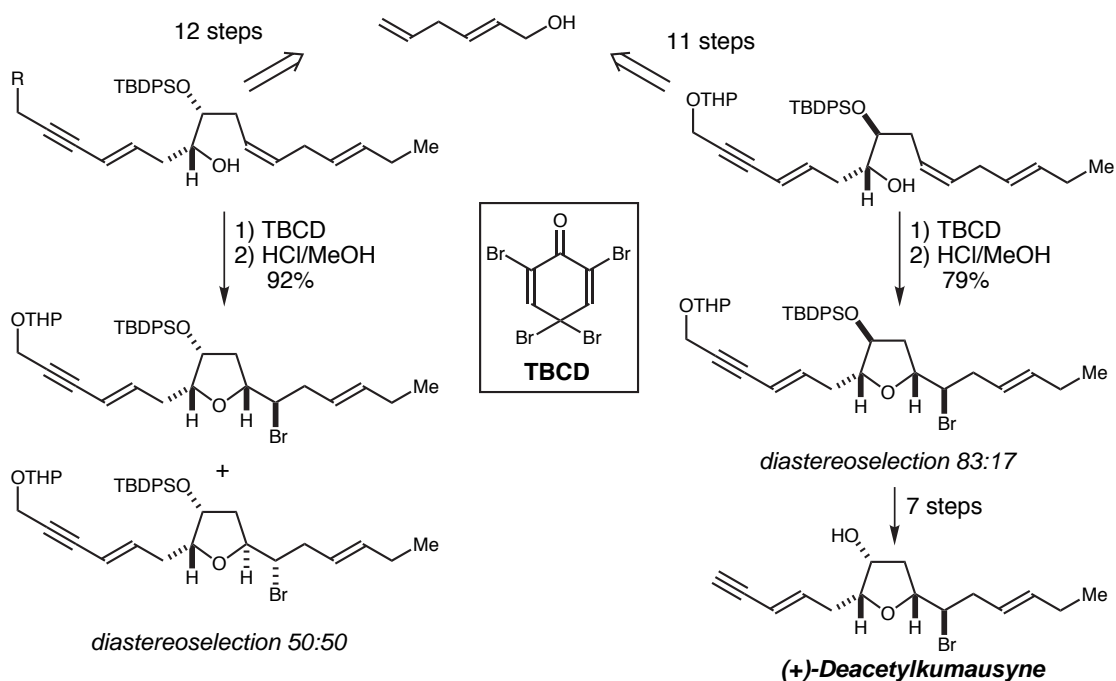


Synthesis of Laurencia Natural Products: Boukouvalas Kumausyne



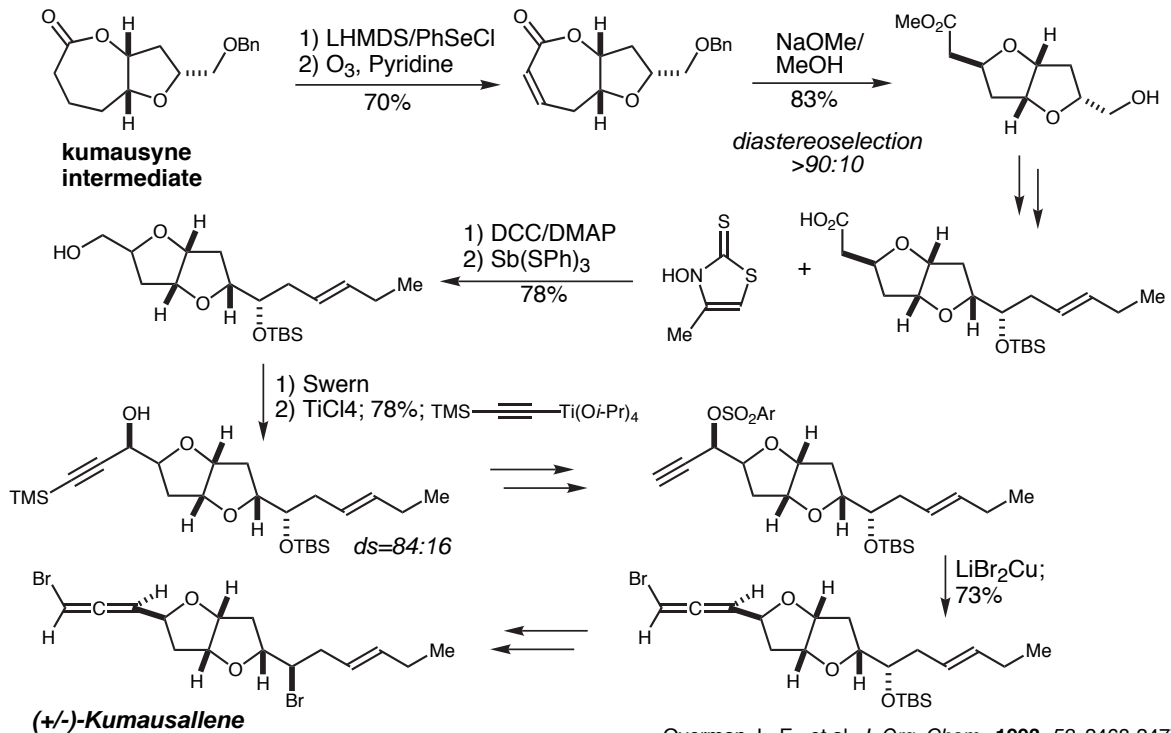
Boukouvalas, J., et al, *J. Org. Chem.*, **1998**, 63, 916-917

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



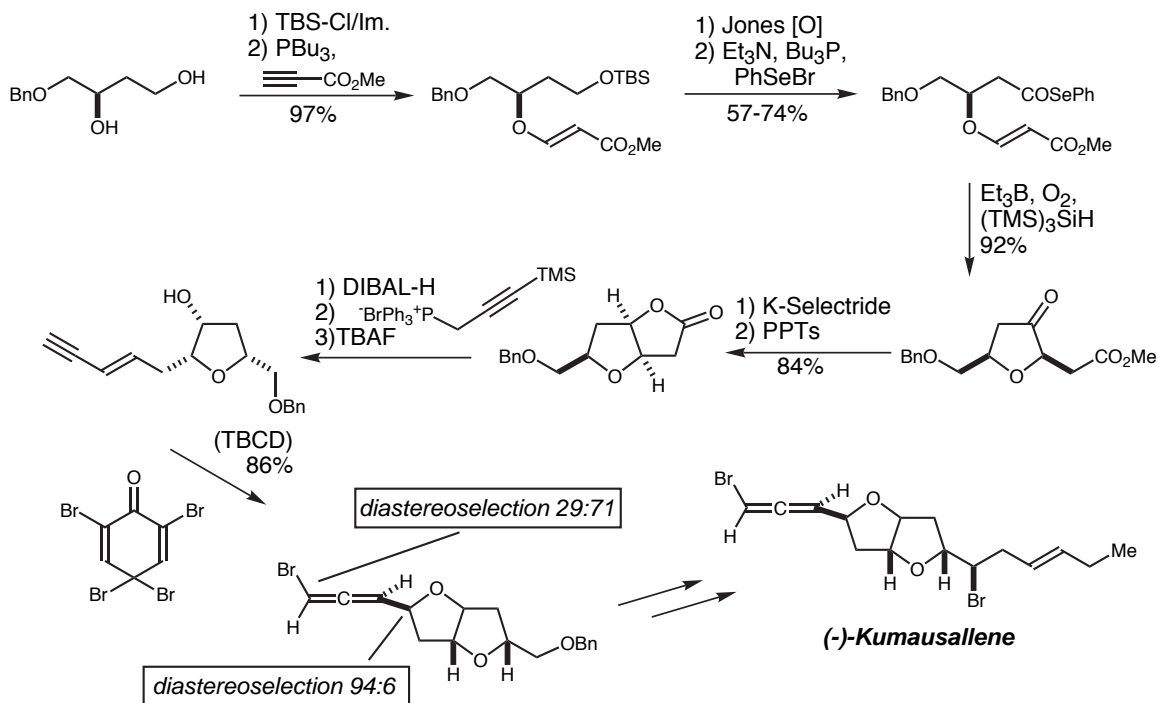
Martín, V. S., et al, *J. Org. Chem.*, **1997**, 62, 1570-1571

Synthesis of Laurencia Natural Products: Overman's Kumausallene



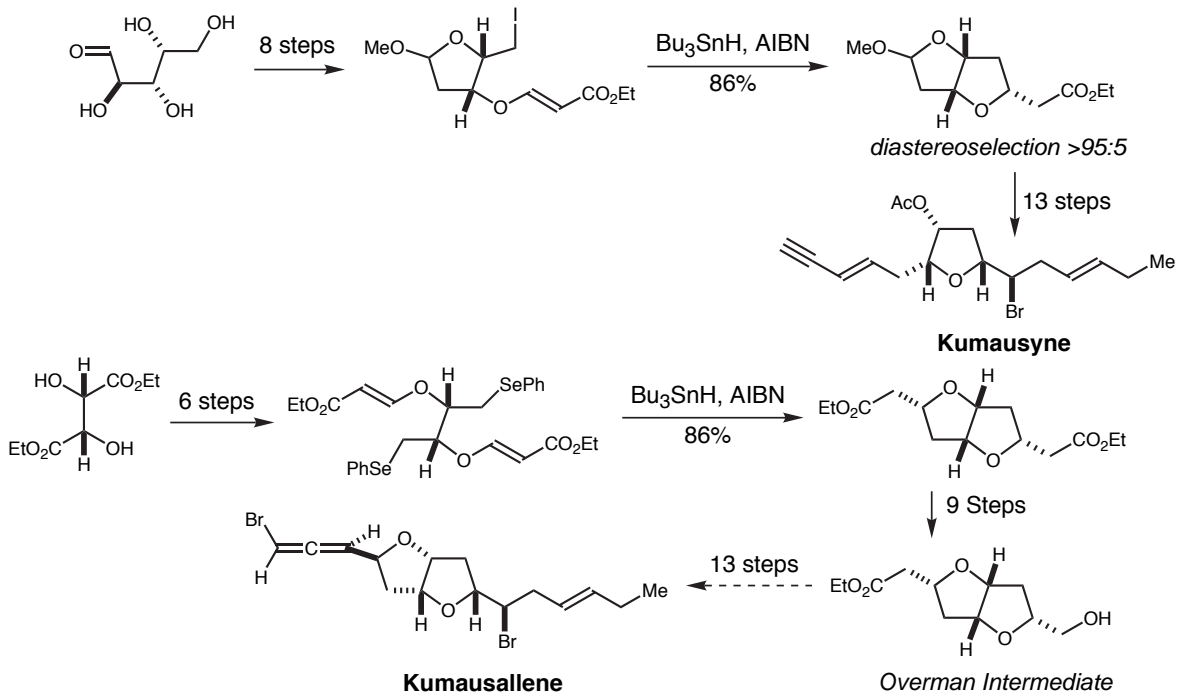
Overman, L. E., et al, *J. Org. Chem.*, **1993**, 58, 2468-2477

Synthesis of Laurencia Natural Products: Evans' Kumausallene



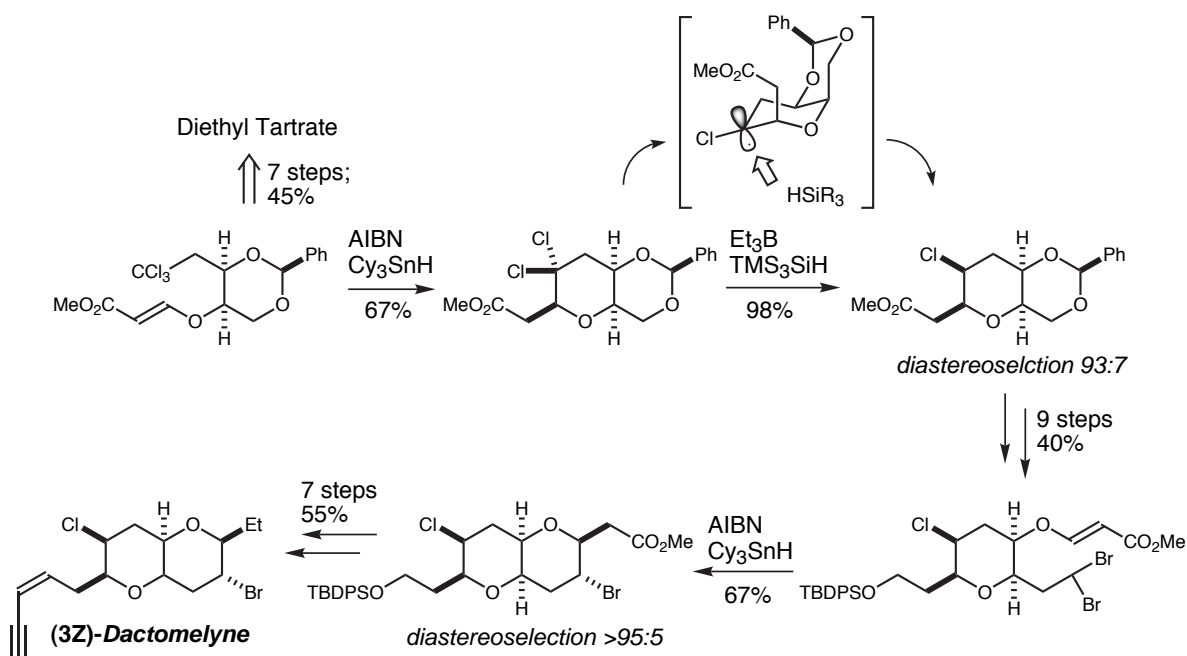
Evans, P. A., et al, *Angew. Chem. Int. Ed.*, **1999**, 38, 3175-3177

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



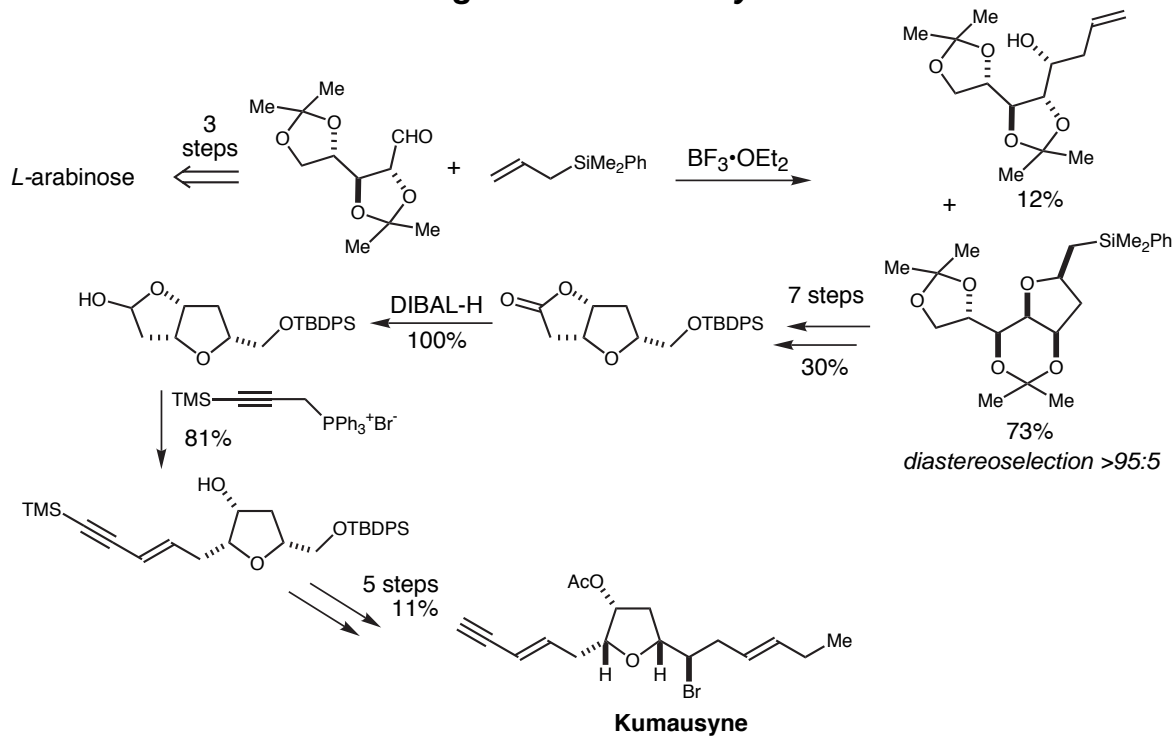
Lee, E, et al, *Tetrahedron Lett*, **1997**, 38, 7757-7758
 Lee, E, et al, *Tetrahedron Lett*, **1998**, 39, 317-318

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



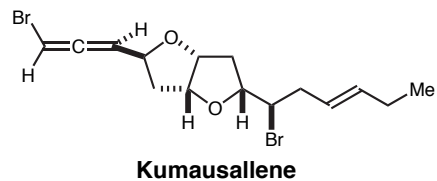
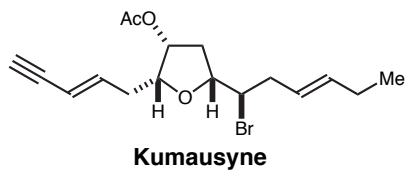
Lee, E, et al, *J. Am. Chem. Soc.*, **1995**, 117, 8017-8017

Synthesis of Laurencia Natural Products: Sugimura's Kumausyne



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

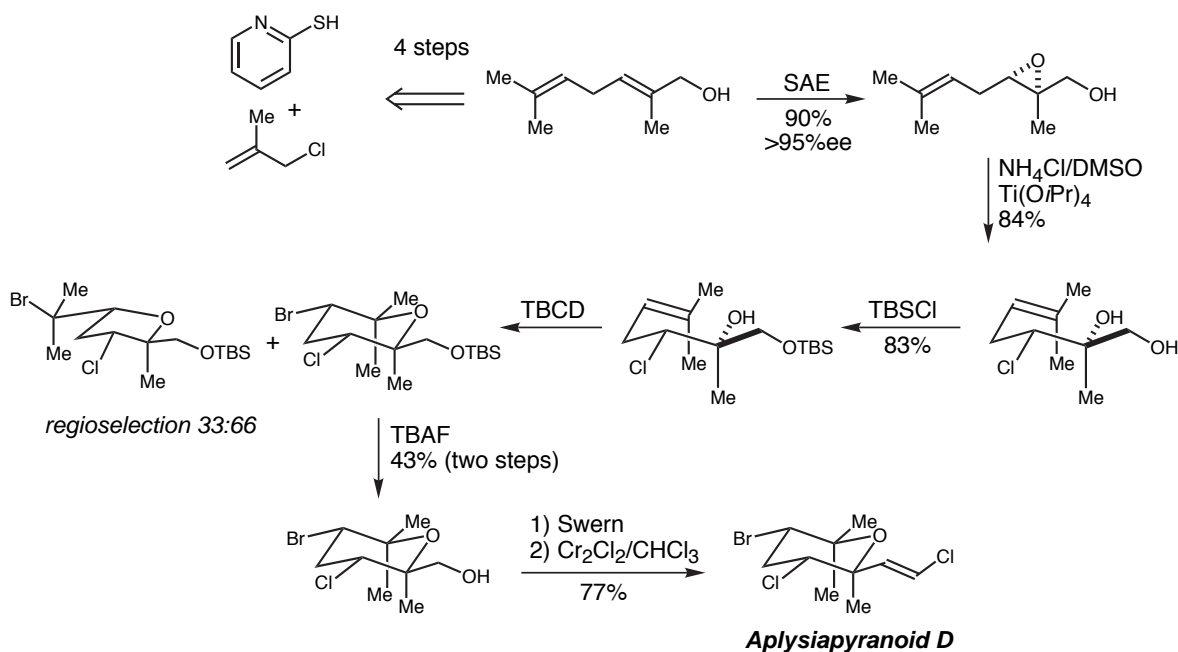
Synthesis of Laurencia Natural Products: Summary of Kumausyne and Kumausallene



	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

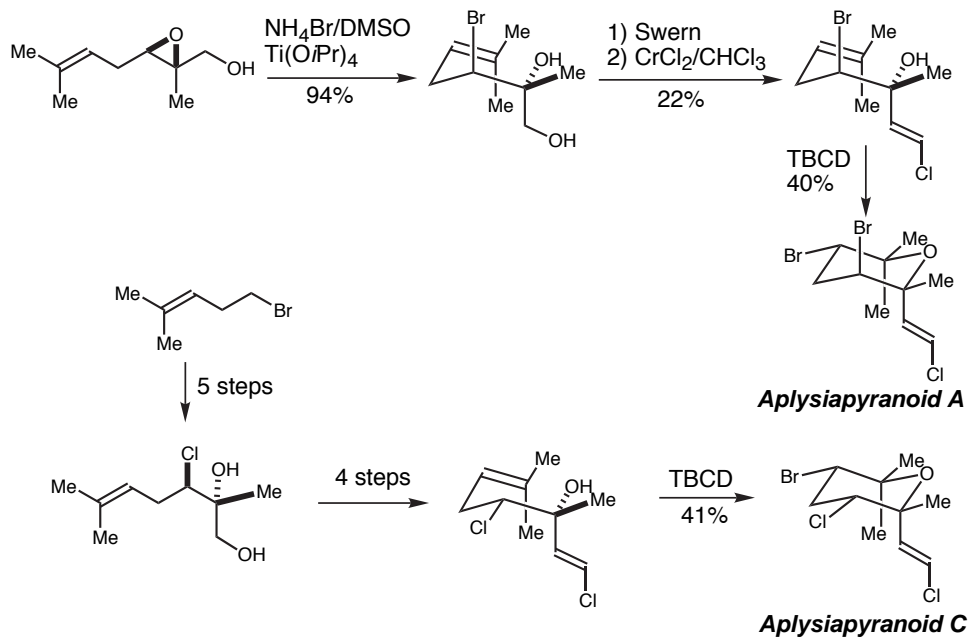
	year	#steps/%yield
Overman	1993	17/2
Lee	1998	29/0.4
Evans	1998	14/6

Synthesis of Aplysia Natural Products: Jung's Aplysiapyranoid D



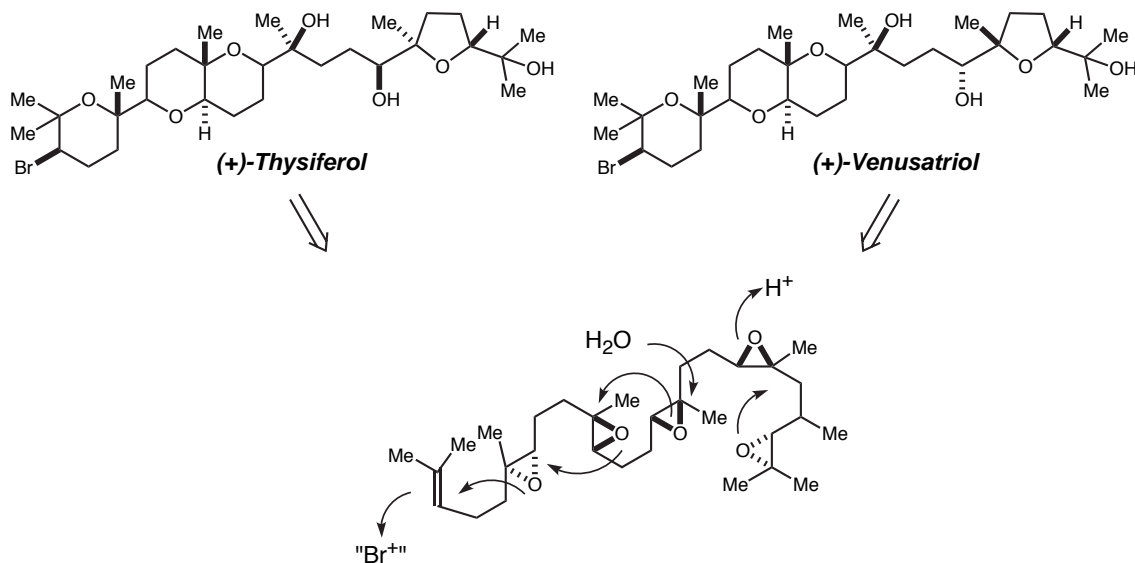
Jung, M. E., et al, *J. Org. Chem.*, **1992**, 56, 1347-1348

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

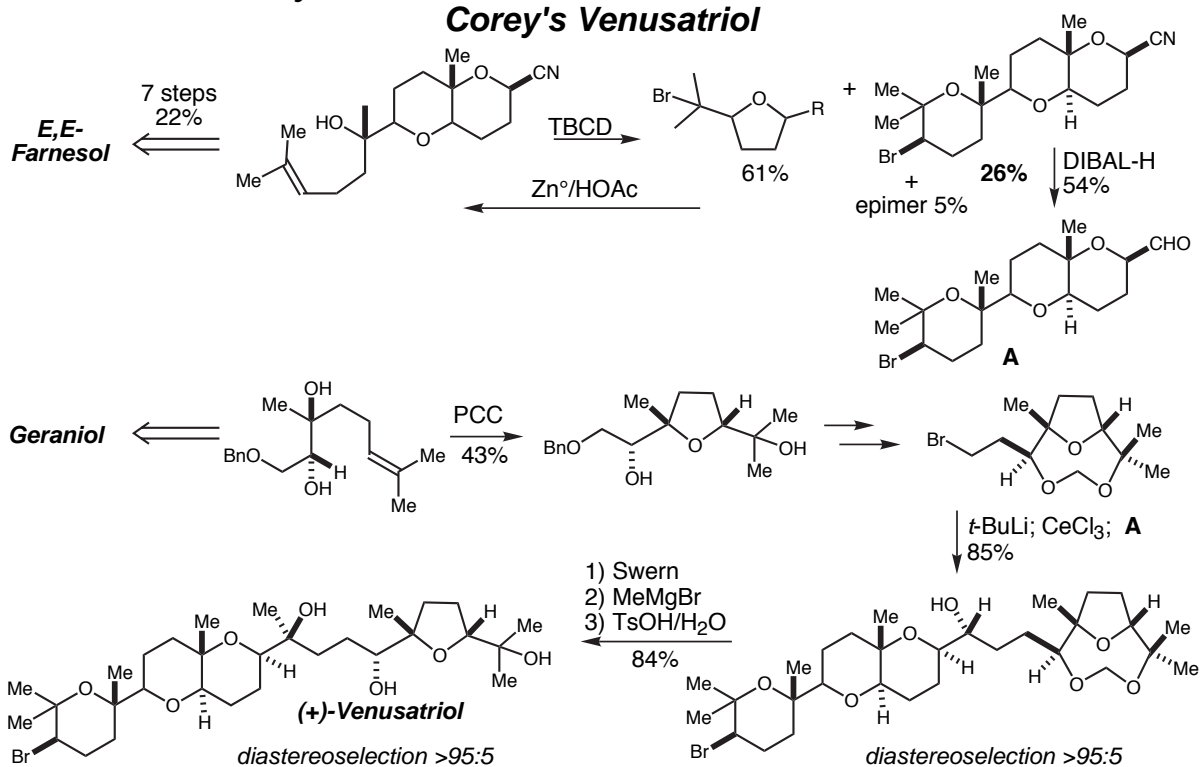


Jung, M. E., et al, *Tetrahedron Lett.*, **1993**, 34, 923-926
Jung, M. E., et al, *J. Org. Chem.*, **1998**, 63, 2982-2987

**Synthesis of Laurencia Natural Products:
Thysiferol & Venusatriol**

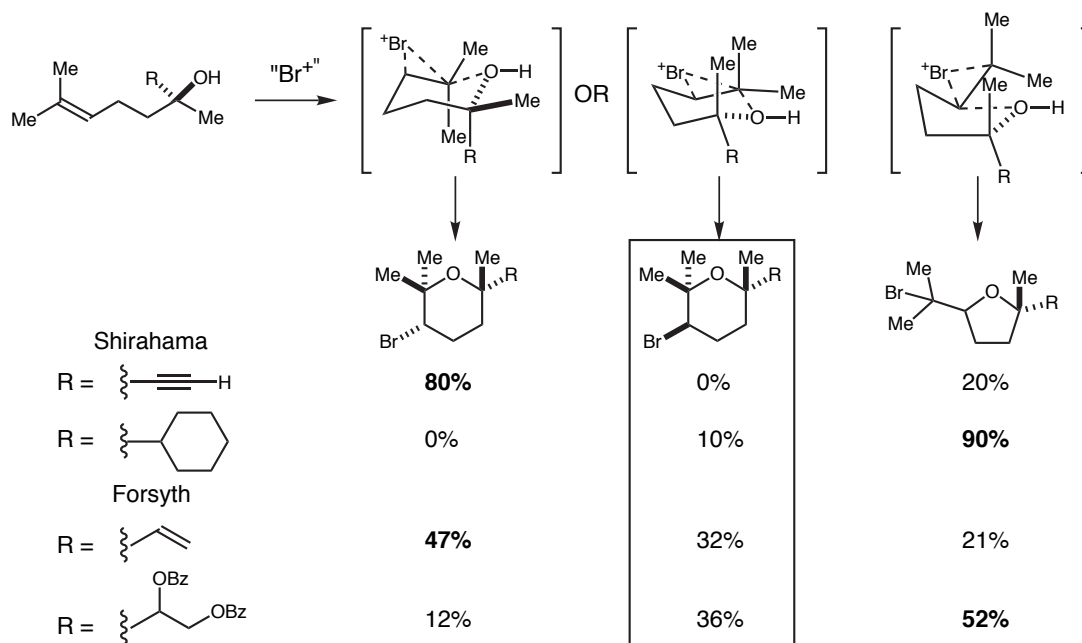


**Synthesis of Laurencia Natural Products:
Corey's Venusatriol**



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

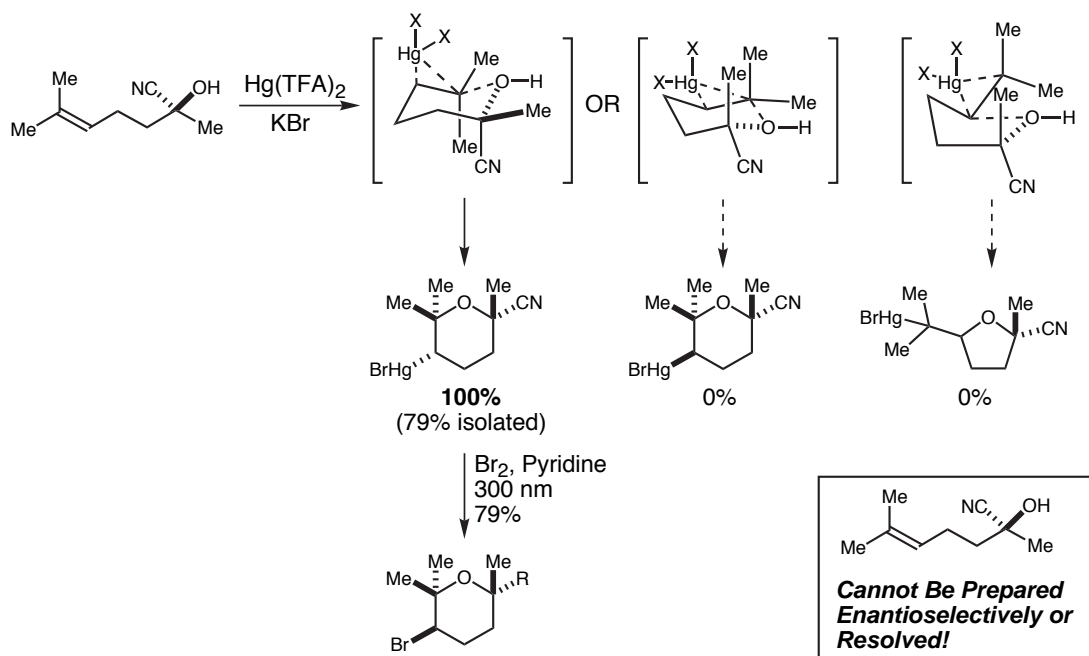
Synthesis of Laurencia Natural Products: Shirahama and Forsyth Improve the Bromocyclization



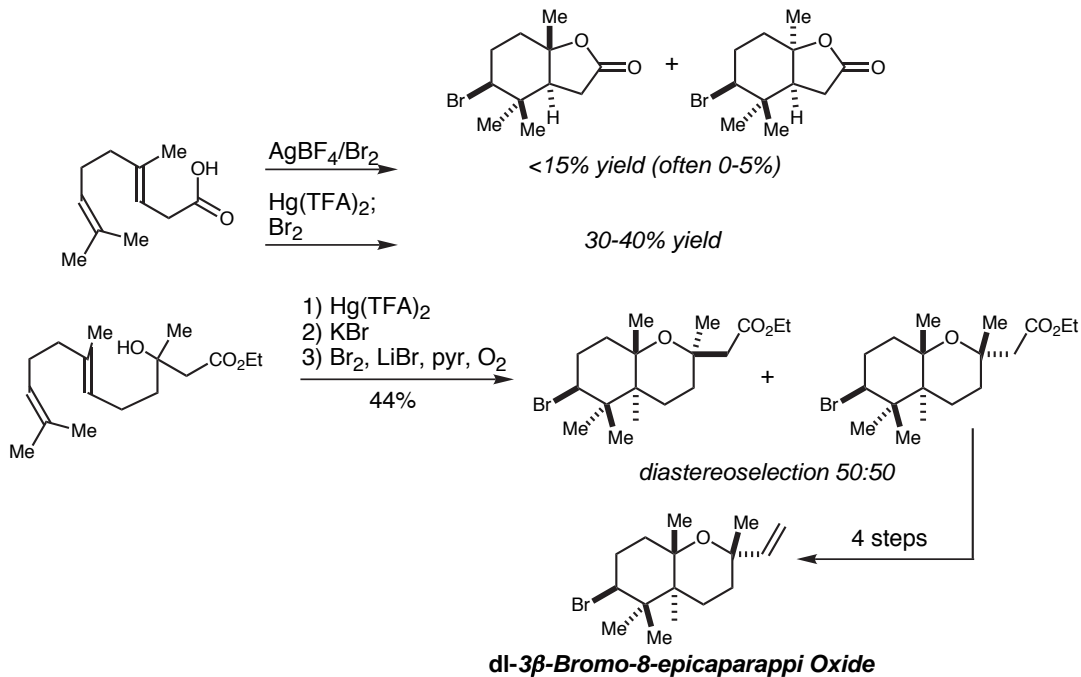
• Bulky R favors correct diastereomer, but also favors THF formation

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

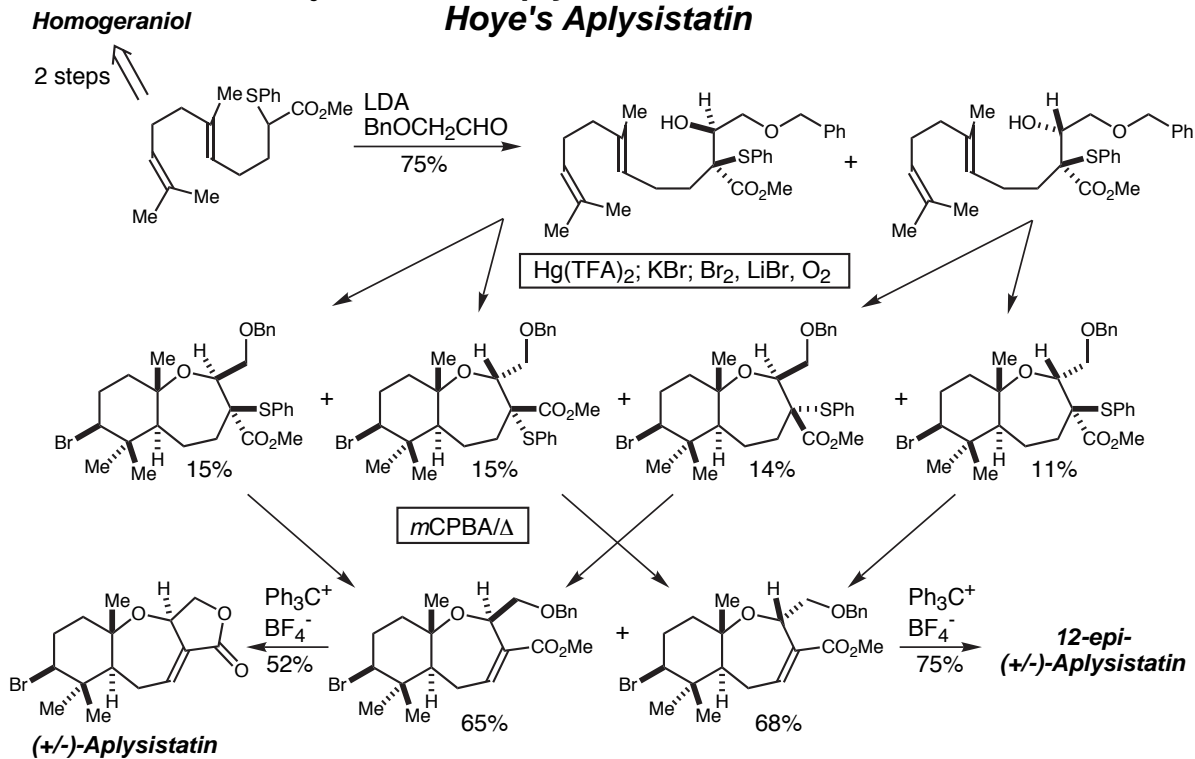


Synthesis of Aplysia Natural Products: Hoye's Polycyclization



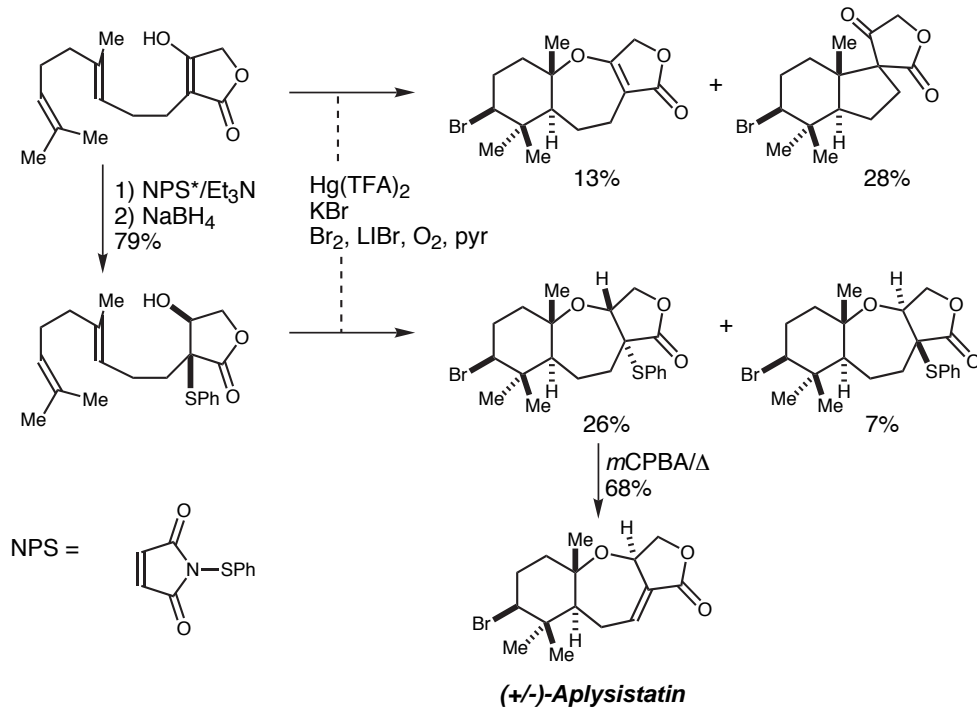
Hoye, T. R., et al, *J. Org. Chem.*, **1978**, *48*, 3693-3697
 Hoye, T. R., et al, *J. Org. Chem.*, **1979**, *49*, 3461-3467

Synthesis of Aplysia Natural Products: Hoye's Aplysistatin



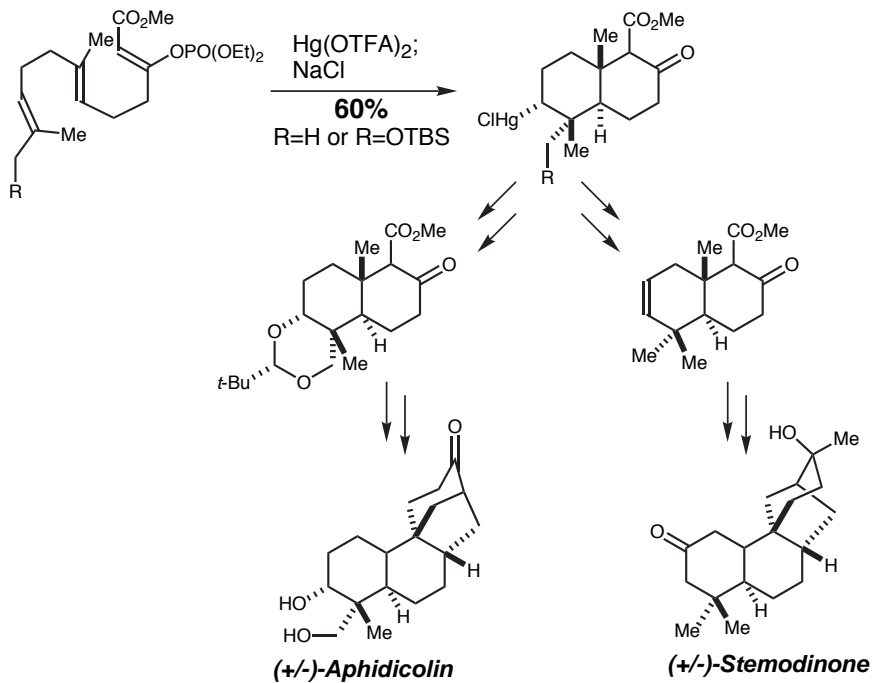
Hoye, T. R., et al, *J. Am. Chem. Soc.*, **1979**, *101*, 5065-5067

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



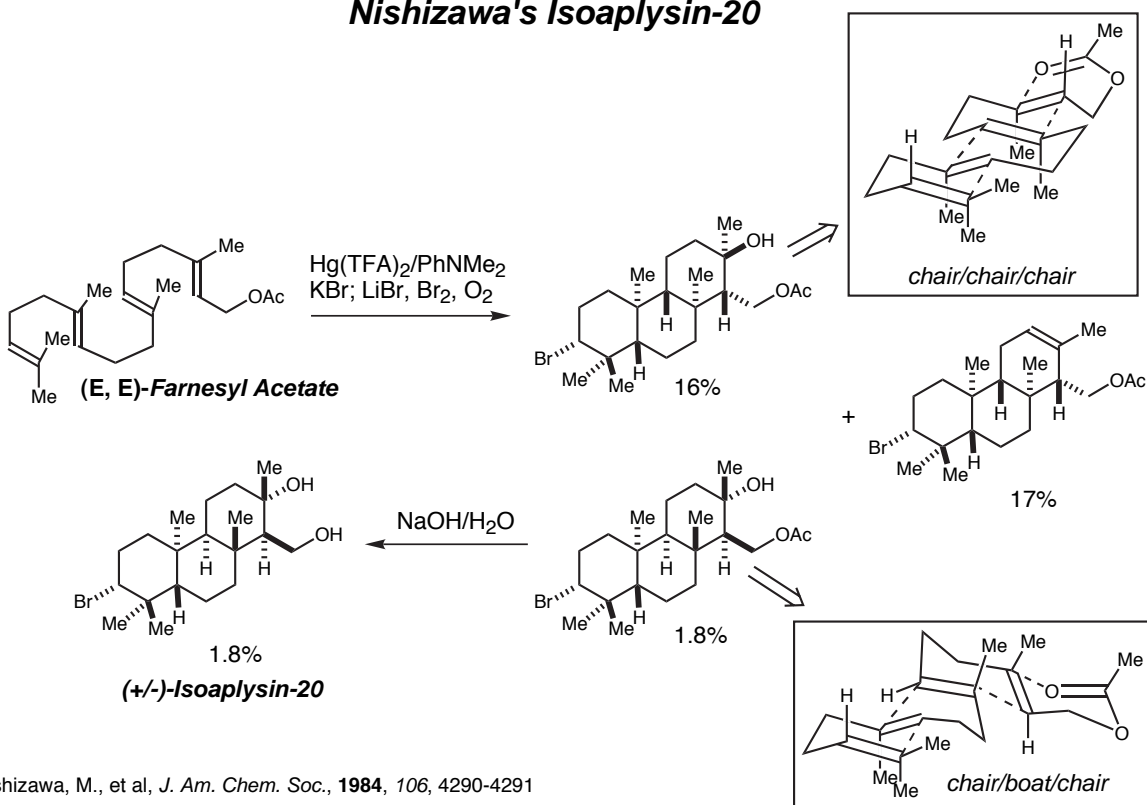
White, J. D., *J. Am. Chem. Soc.*, **1982**, 104, 3923-3928

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

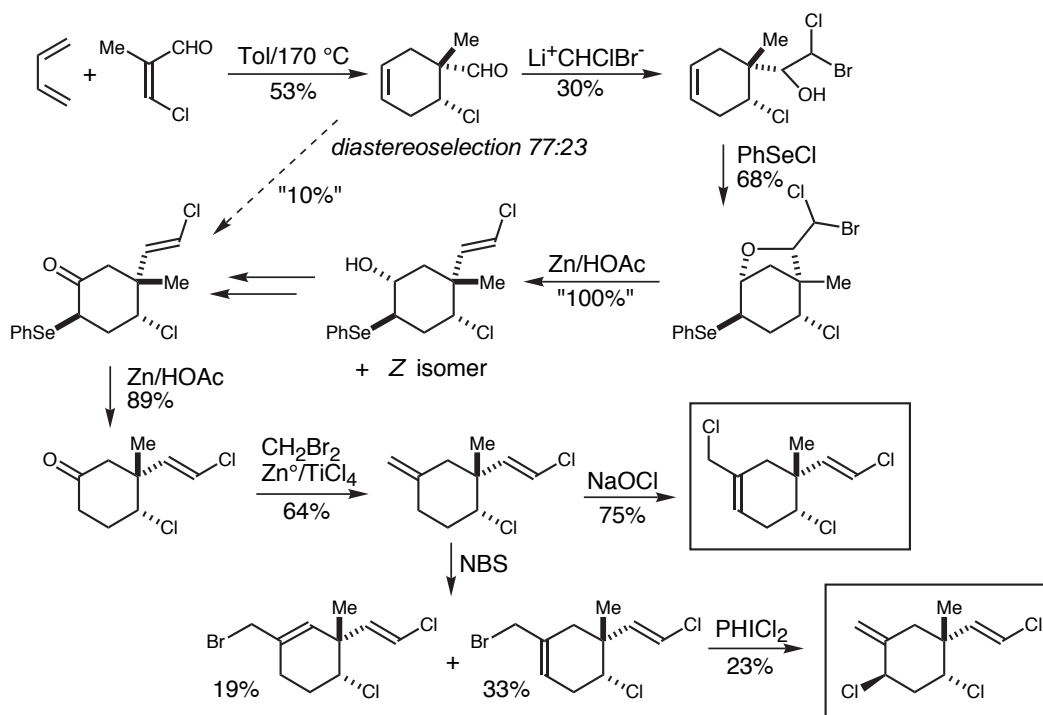


Corey, E. J. et al, *J. Am. Chem. Soc.*, **1980**, 102, 1742-1744
Corey, E. J. et al, *J. Am. Chem. Soc.*, **1980**, 102, 7612-7613

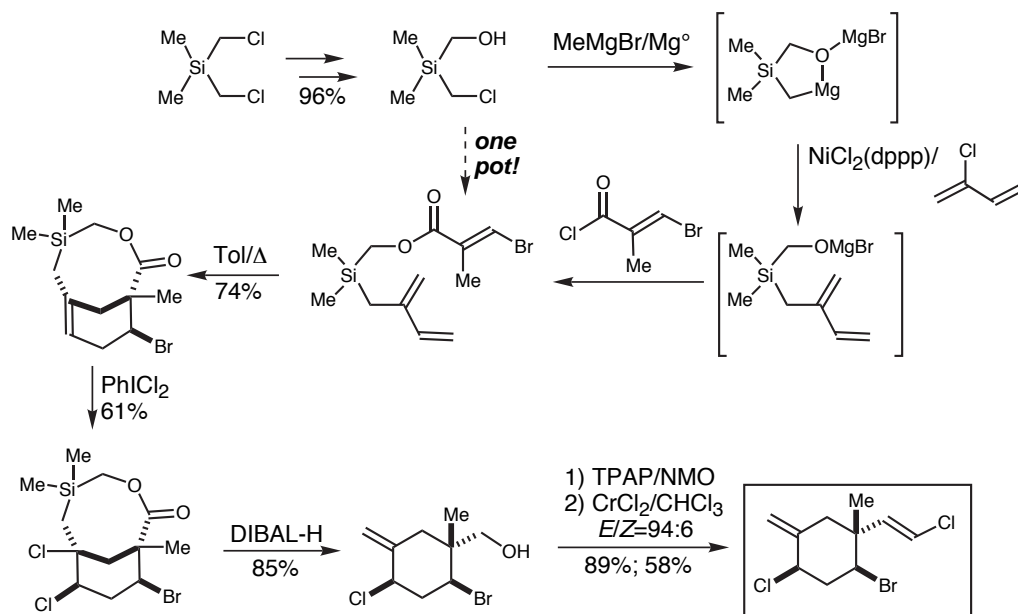
**Synthesis of Laurencia Natural Products:
Nishizawa's Isoaplysin-20**



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

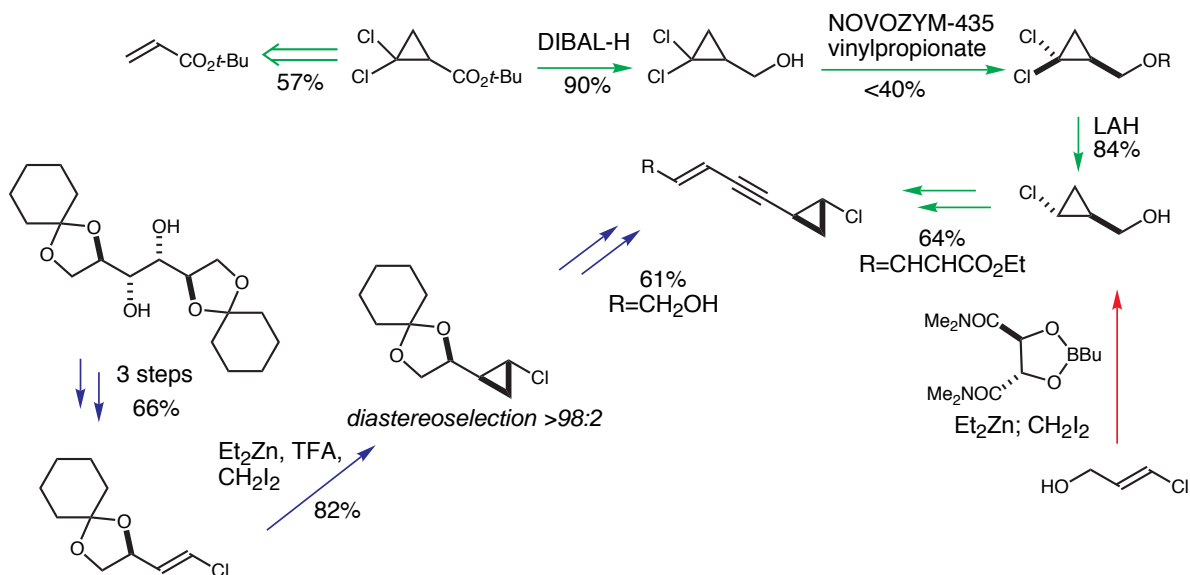


Synthesis of Plocamium Natural Products: Shea's T2IM Diels-Alder Approach



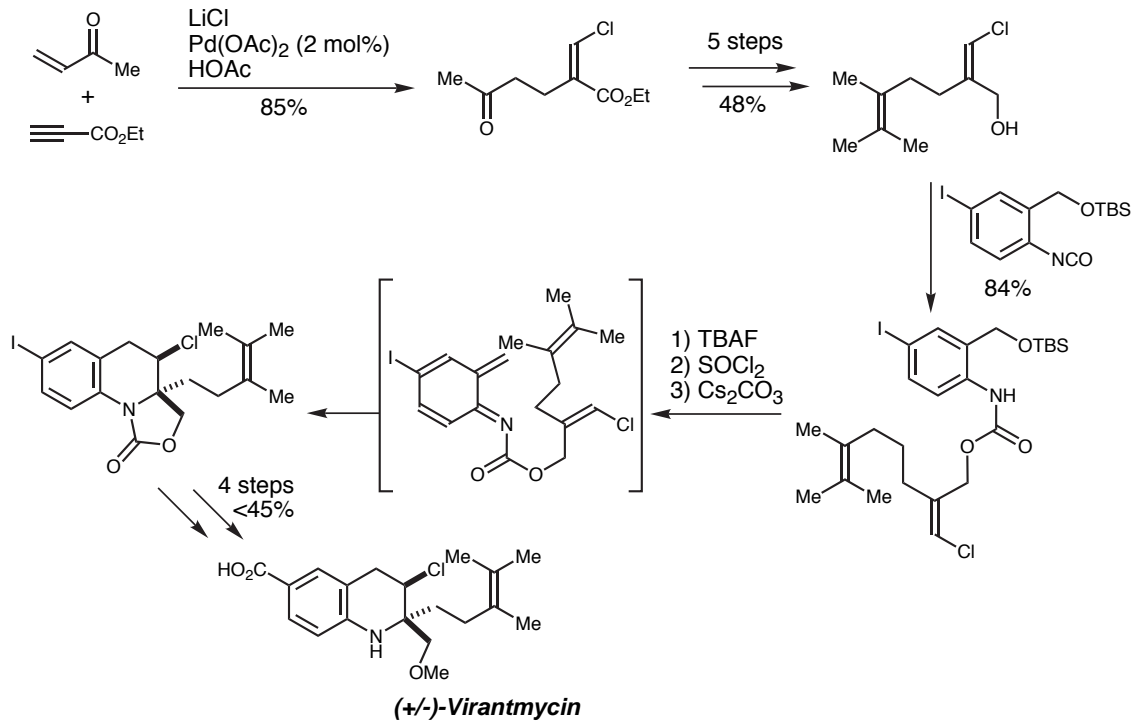
Shea, K. J., et al, *J. Org. Chem.*, **1997**, 62, 8962-8963

Synthesis of Callipeltoside Sidechain: Chloroalkene Cyclopropanation



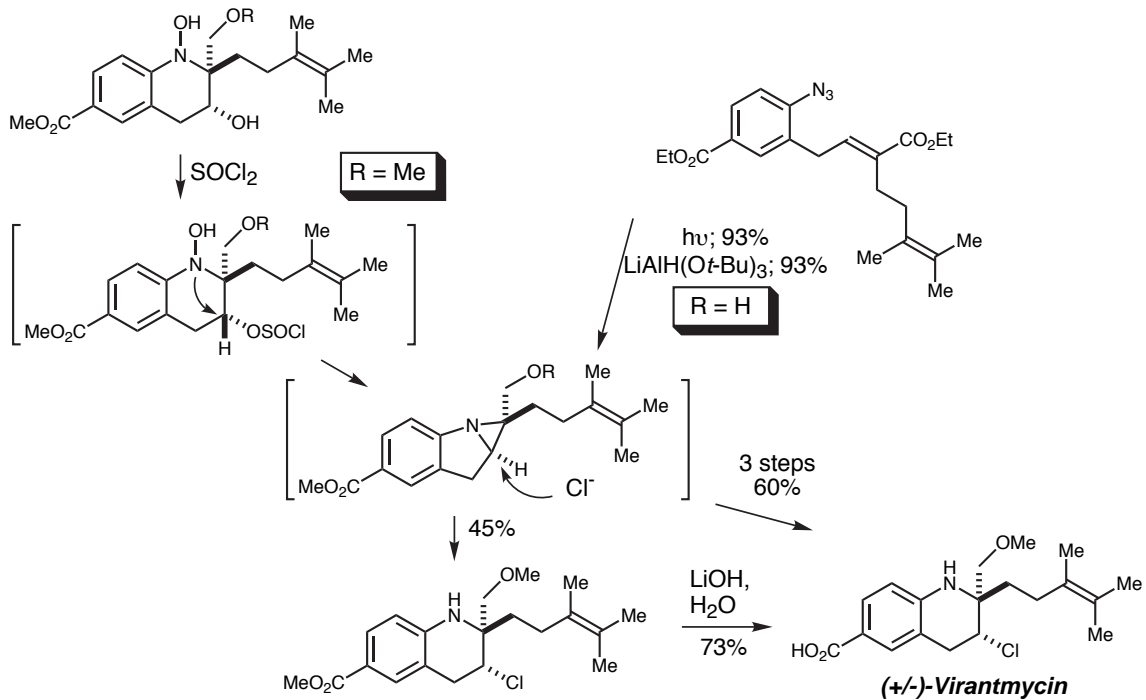
Olivo, H., et al, *Org. Lett.*, **2001**, 2, 4055-4058
 Evans, D. A., et al, *Org. Lett.*, **2001**, 3, 503-505
 Patterson, I., et al, *Angew. Chem. Int. Ed.*, **2001**, 603-607

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



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

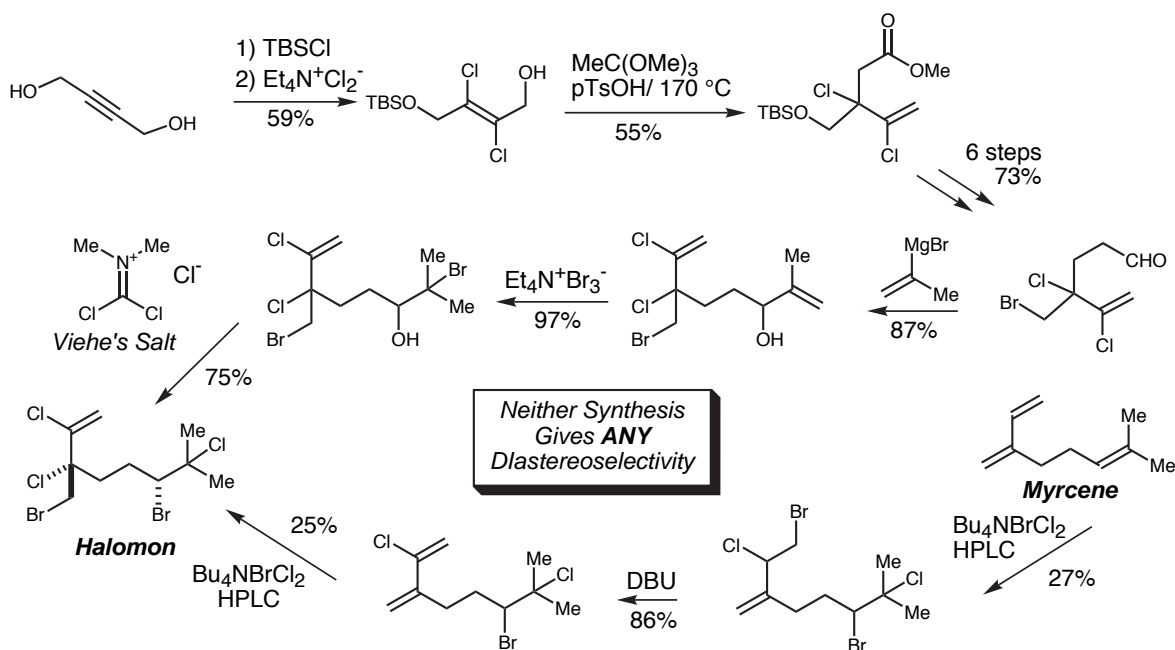
**Synthesis of Virantmycin:
Previous Syntheses by Raphael and Shirahama**



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

Halomon: The Final Frontier

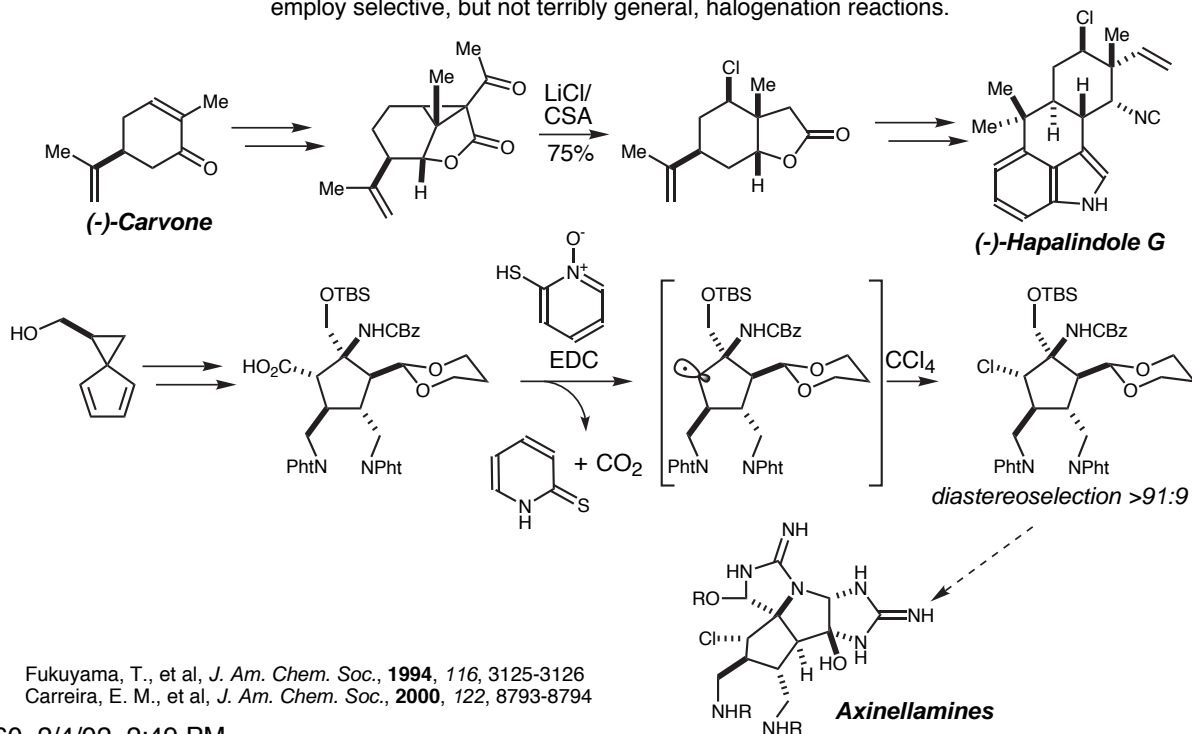
- The biggest challenge in HNP synthesis is the preparation of acyclic halogenated terpenes
- Only two syntheses of Halomon have been reported, and there is still much room for improvement



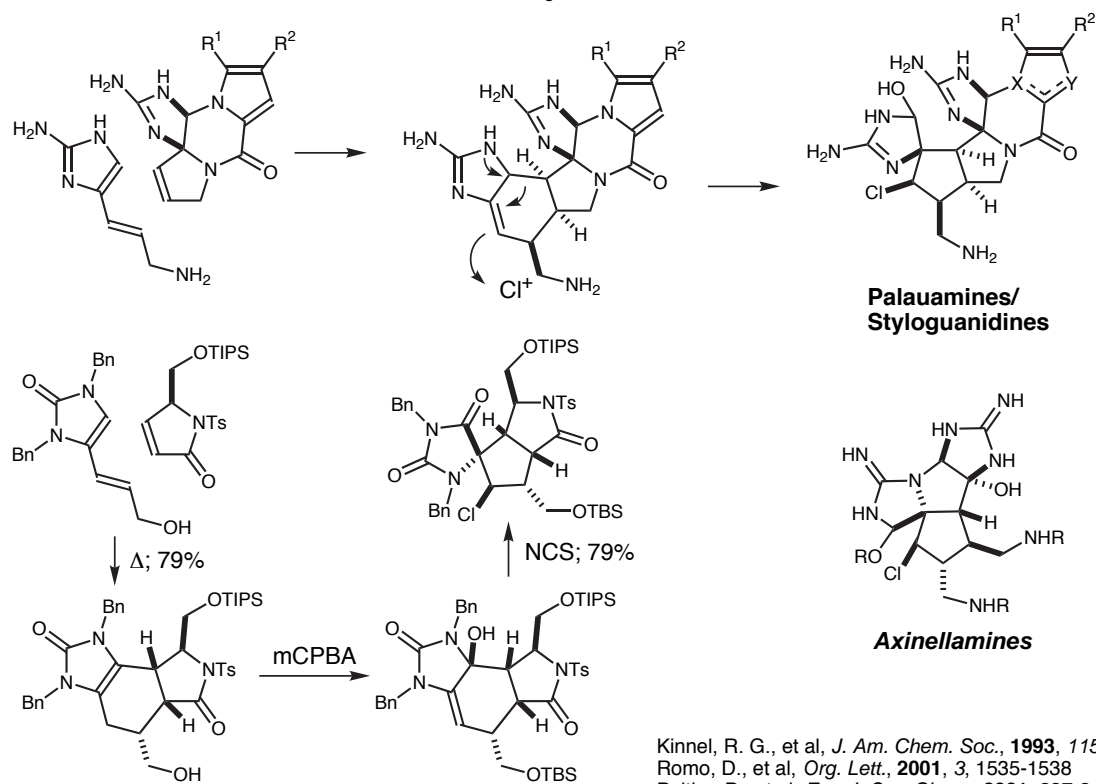
Mioskowski, C., et al, *Angew. Chem. Int. Ed.*, **1998**, 37, 2085-2086
Hirama, M., et al, *Angew. Chem. Int. Ed.*, **2000**, 39, 3430-3431

Outliers

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



Outliers II



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