Shi Asymmetric Epoxidation Reaction

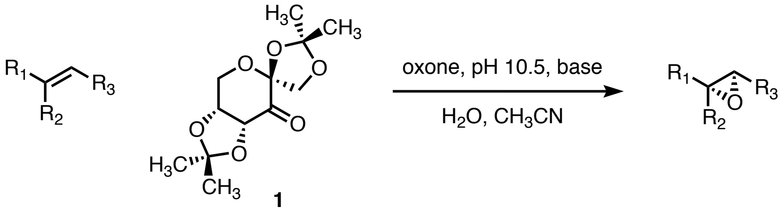
Reviews:

Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958–3987.

Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.

Frohn, M.; Shi, Y. *Synthesis* **2000**, *14*, 1979–2000.

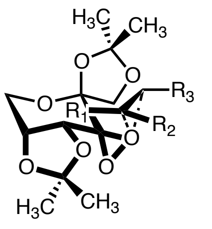
General Transformation:



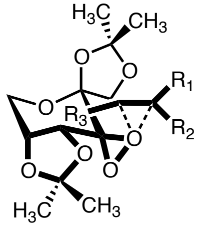
- Useful for epoxidation of *trans*-disubstituted olefins (ketone **1**), trisubstituted olefins (ketone **1**), conjugated *cis*-disubstituted olefins (ketone **2**, see p. 3), and styrenes (ketone **2**, see p. 3).

Catalyst Conditions:

- Ketone **1** can be readily prepared from *D*-fructose ($15/kg) by ketalization (acetone, $HClO_4$, 0 °C, 53%) and oxidation (PCC, 23 °C, 93%). *L*-Fructose can be prepared in 3 steps from readily available *L*-sorbose.
- Ketone **1** can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1 $KHSO_5$:$KHSO_4$:K_2SO_4) is used as the stoichiometric oxidant but H_2O_2/CH_3CN can also be used (peroxyimidic acid is the proposed oxidant).
- Generally, the optimum pH for dioxirane epoxidation is 7–8. At higher pH, Oxone tends to decompose. However, at pH 7–8 the Shi catalyst decomposes due to competing Baeyer-Villiger reaction. By increasing the pH to 10.5 (by addition of K_2CO_3), the amount of ketone used can be reduced to a catalytic amount (30 mol %) and the amount of Oxone can be reduced to a stoichiometric amount (1.5 equiv), suggesting that at this pH the ketone is sufficiently reactive to compete with Oxone decomposition.
- Dimethoxymethane (DMM) and CH_3CN (2:1 v/v) solvent mixtures generally provide higher ee's.
- Reaction temperatures range from –10 to 20 °C.
- It is proposed that the Shi epoxidation proceeds through a dioxirane intermediate and a spiro transition state and that a so-called planar transition state is a main competing pathway. The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the π* orbital of the olefin.



Spiro

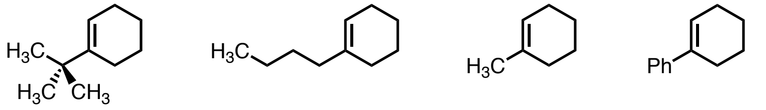


Planar

Higher ee's are observed with smaller R_1 and larger R_3 substituents.

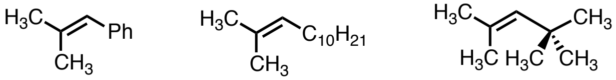
Examples:

1. Effect of smaller R_1 (also known as "T-branch"; phenyl groups can be considered smaller than methyl).



26% ee 79% ee 81% ee 98% ee

2. Effect of larger R_3 (also: "L-branch").



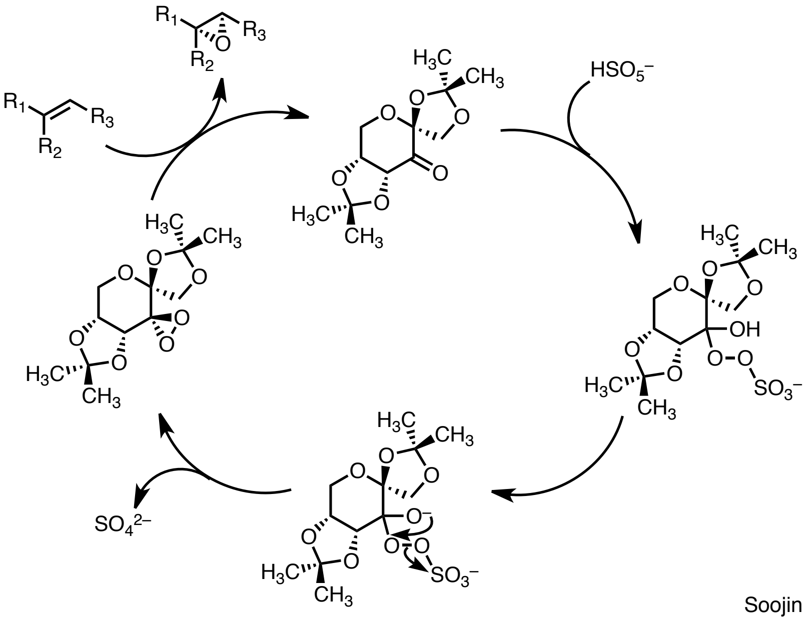
76% ee 86% ee 91% ee

3. Comparing the size of R_1 and R_3.

76% ee 97% ee

Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *19*, 11224–11235.

Proposed Catalytic Cycle:



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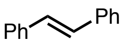
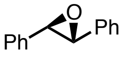
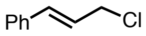
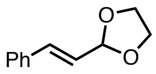
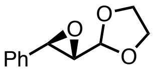
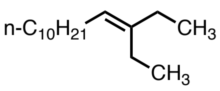
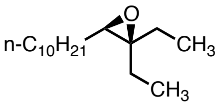
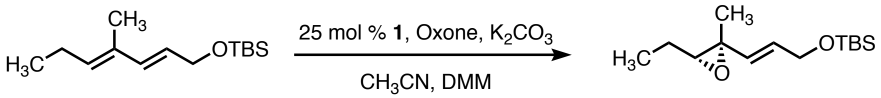
Examples of Shi Epoxidations:

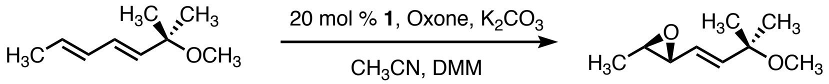
Substrate	Product	Yield	ee (%)
		73%	95%
		61%	93%
		41%	93%
		94%	89%

Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807
and Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

- Monoepoxidation of conjugated dienes favors the more electron-rich or less sterically hindered olefin. The amount of catalyst used must be properly controlled (0.2–0.3 equiv) to prevent bis-epoxidation. Vinyl silanes and allylic silyl ethers are deactivated towards epoxidation (attributed to sterics and inductive deactivation, respectively).

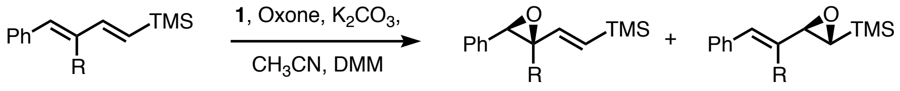


81%, 96% ee



65%, 89% ee

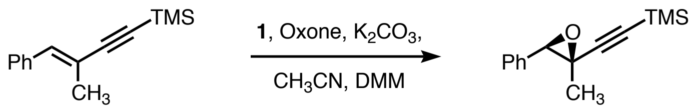
- Regioselectivity increases when either olefin of a 1,3-diene is trisubstituted. It is proposed that the trisubstituted olefin prevents full conjugation of the diene due to $A_{1,2}$ strain, causing each olefin to present an individual steric or electronic environment, as if each were isolated.



	Yield	ee	Ratio
R = H	31%	95%	1:1
R = CH_3	77%	92%	14:1

Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948–2953.

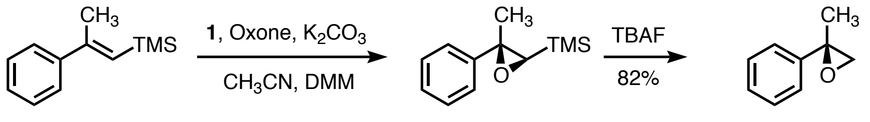
- Epoxidation of enynes occurs selectively at the C–C double bond.



64%, 94% ee

Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425–4428.
Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646–7650.

- 1,1-Disubstituted epoxides can be synthesized enantioselectively by Shi epoxidation of trisubstituted vinyl silanes followed by TBAF-mediated desilyation.



74%, 94% ee

94% ee

Warren, J.D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675–7677.

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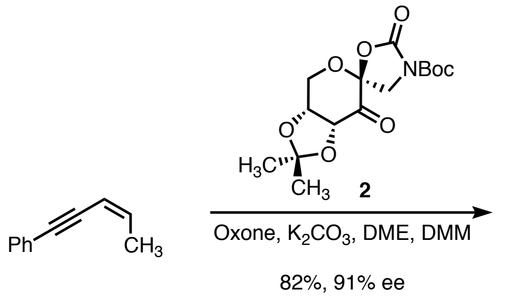
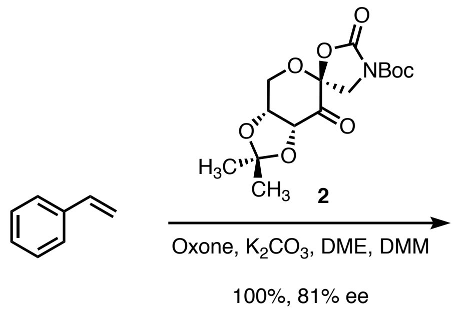
- A modified catalyst is useful for epoxidation of *cis*-disubstituted olefins and styrenes.



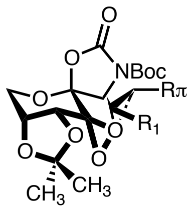
The enantiomeric excess is generally high for cyclic olefins and for acyclic olefins conjugated with an alkynyl or aromatic group.

Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551–11552.

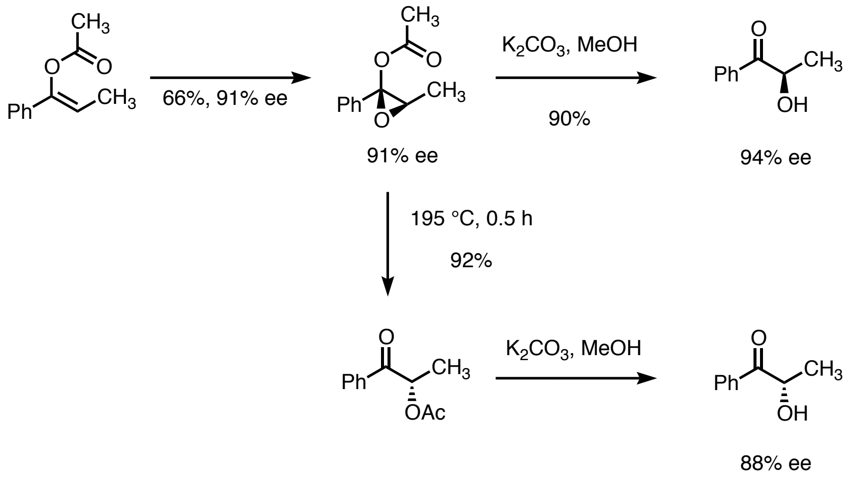


Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929–1931.
Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435–2446.

In both cases, it is proposed that the π-substituent of the substrate prefers to be proximal to the spiro oxazolidinone.

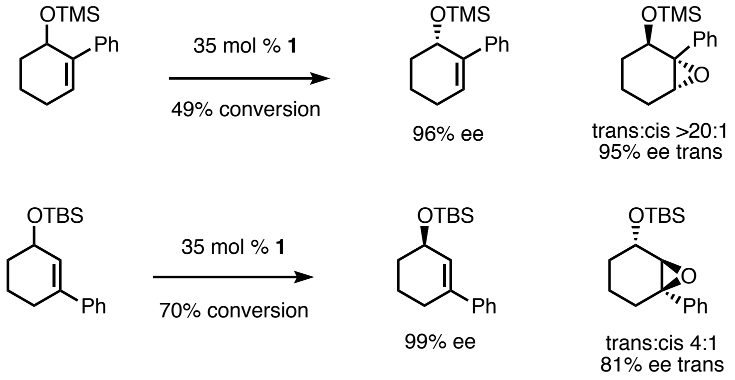


- Enol esters can be used as substrates for the preparation of α-hydroxyketones in either enantiomeric form.



Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819–7822.

- Kinetic resolution of racemic 1,3- and 1,6-disubstituted cyclohexenes can provide optically enriched allylic silyl ethers.



Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718–7719.

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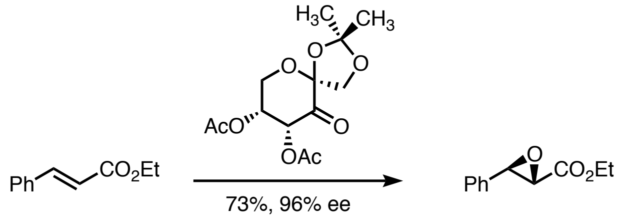
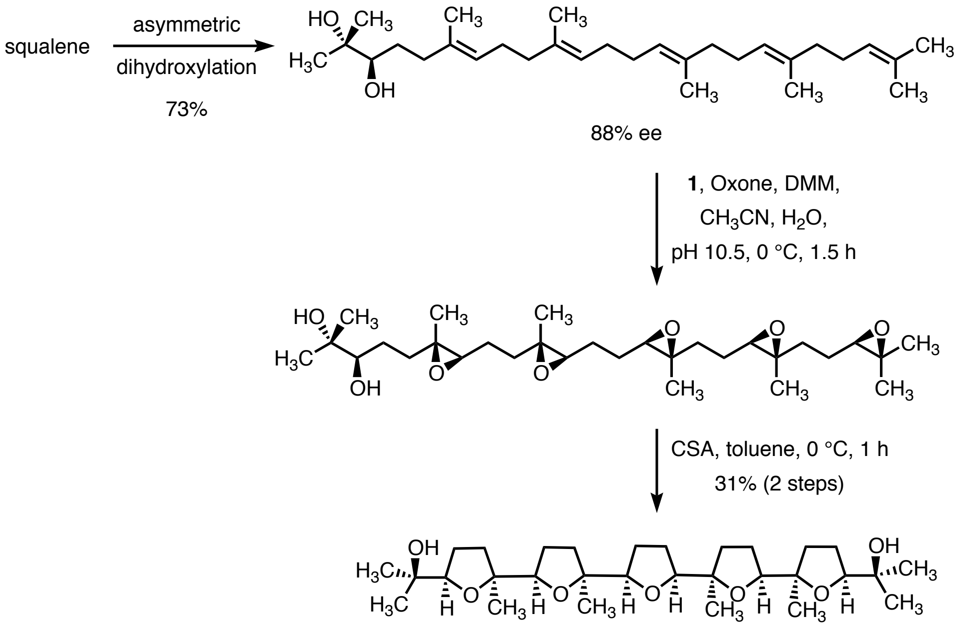
- The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient α,β-unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.


73%, 96% ee

Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792–8793.

Applications in Synthesis:

Glabrescol:


squalene

asymmetric dihydroxylation

73%

88% ee

1, Oxone, DMM, CH_3CN, H_2O, pH 10.5, 0 °C, 1.5 h

CSA, toluene, 0 °C, 1 h

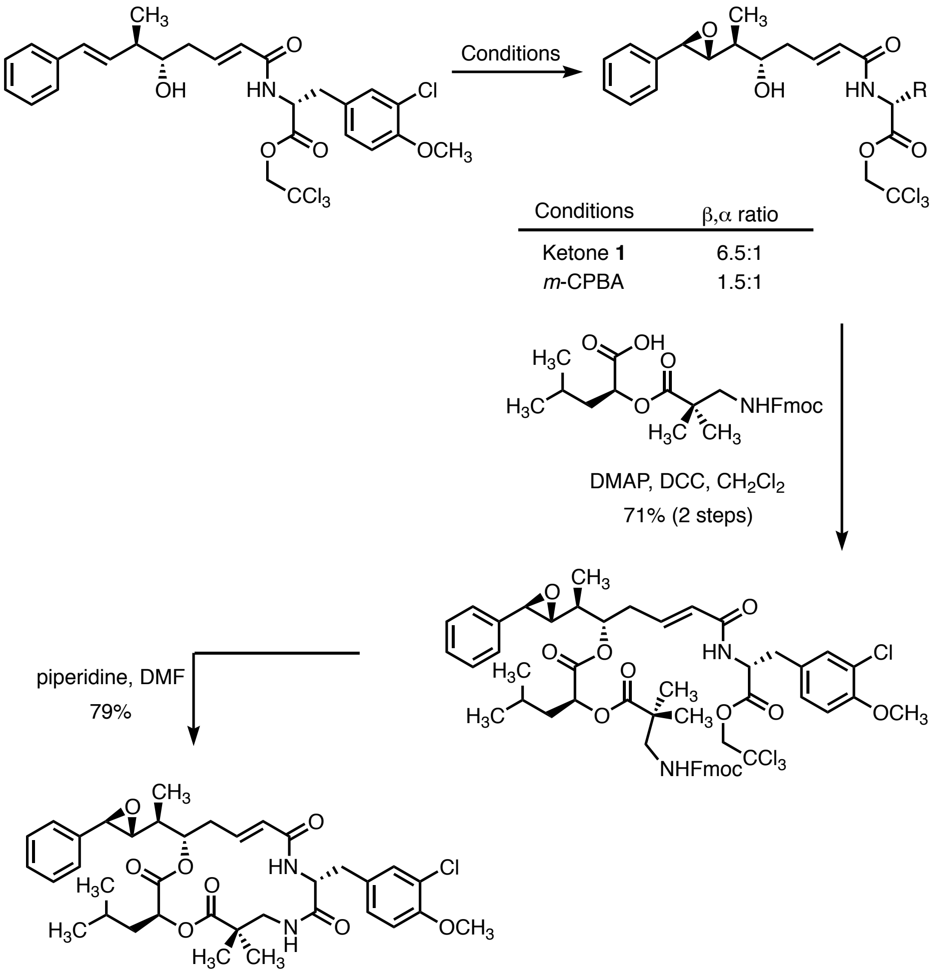
31% (2 steps)

originally proposed structure of Glabrescol

Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831–4832.

Cryptophycin 52:

The Shi epoxidation system provided the desired epoxide in a 6:1 diastereomeric ratio, while other epoxidation methods never exceeded a 2:1 ratio.


Conditions

Conditions	β,α ratio
Ketone **1**	6.5:1
m-CPBA	1.5:1

DMAP, DCC, CH_2Cl_2

71% (2 steps)

piperidine, DMF

79%

Cryptophycin 52

Hoard, D. W.; Moher, E. D.; Martinelli, M. J.; Norman, B. H. *Org. Lett.* **2002**, *4*, 1813–1815.

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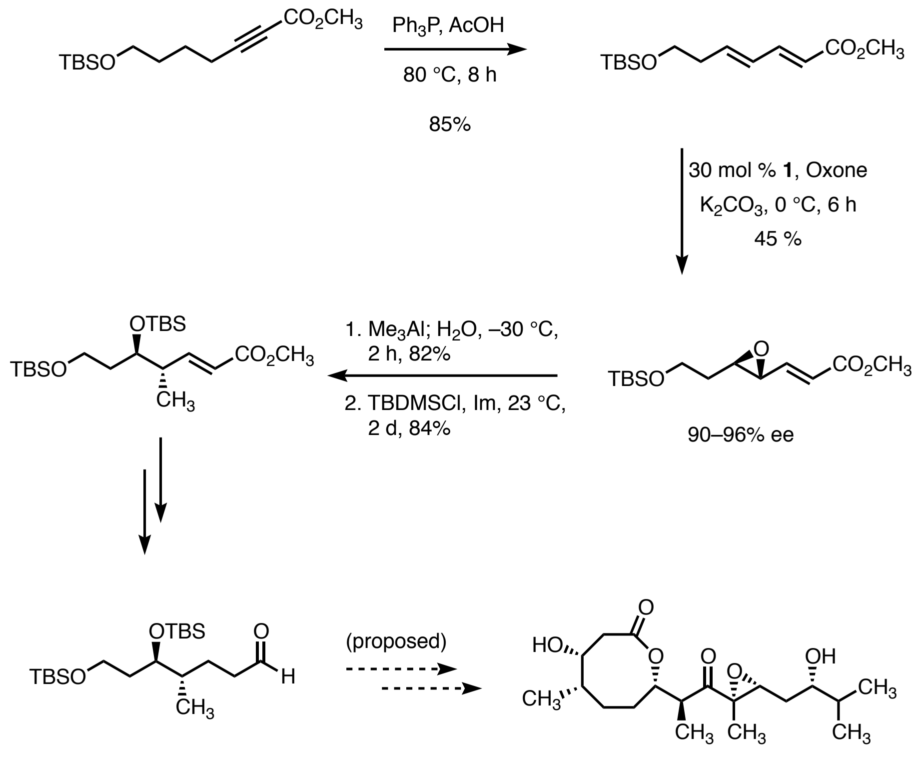
Octalactin A:

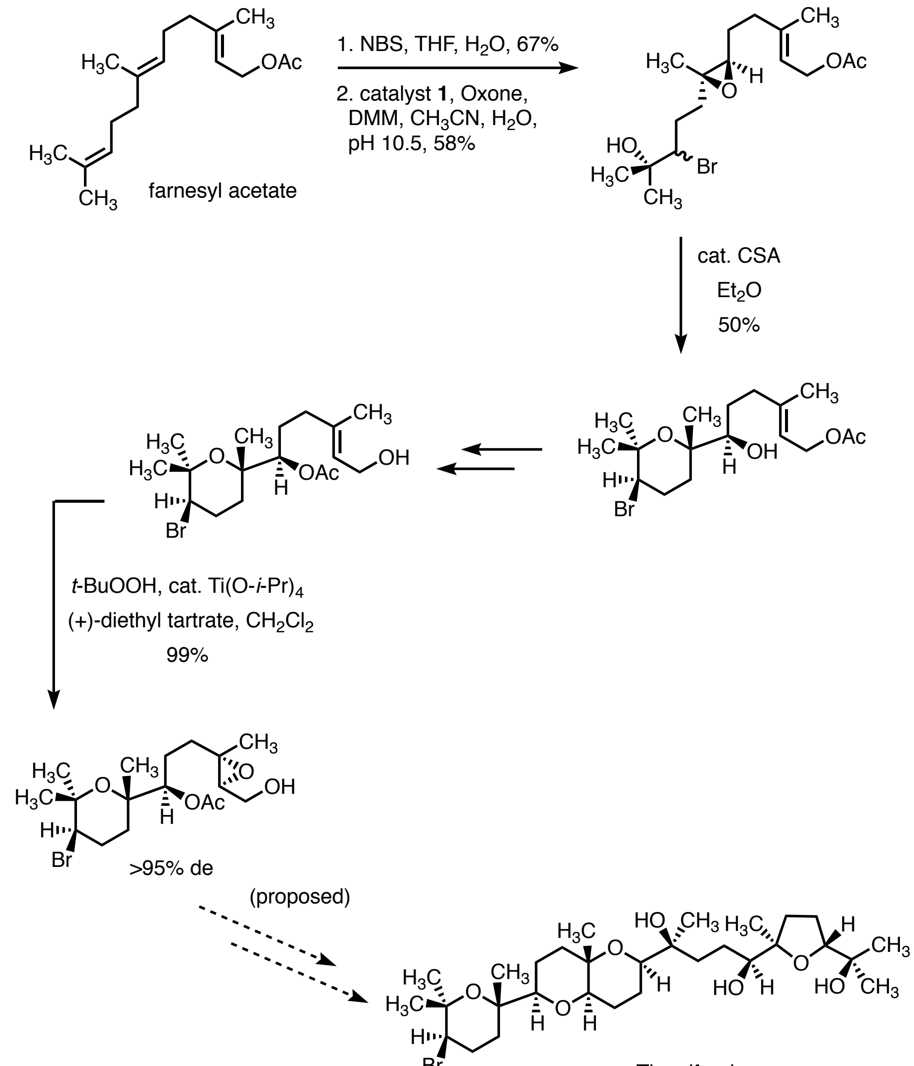


Octalactin A

Bluet, G.; Campagne, J.-M. *Synlett* **2000**, *1*, 221–222.

Thyrsiferol:

Post epoxidation, only one bromohydrin diastereomer cyclized to the bromotetrahydropyran. The unreactive diastereomer was separated from the cyclization product and isolated in 30% yield.



Thyrsiferol

McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595.

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