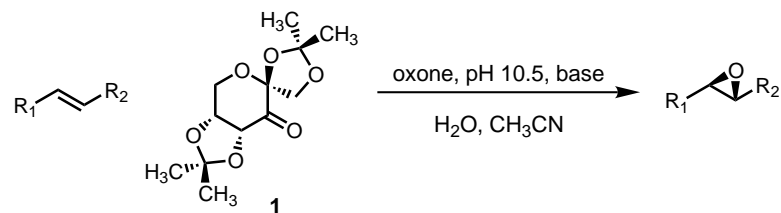


## Reviews:

Wang, Z.-X.; Tu, W.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

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

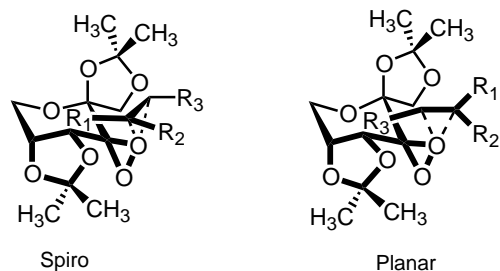
## General Transformation:



- 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:

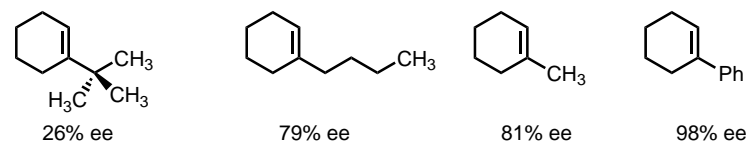
- Ketone **1** can be readily prepared from *D*-fructose (\$15/kg) by ketalization (acetone,  $\text{HClO}_4$ , 0 °C, 53%) and oxidation (PCC, 23 °C, 93%). *L*-Fructose can be prepared in 3 steps from readily available *L*-sorbitol.
- Ketone **1** can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1  $\text{KHSO}_5\text{:KHSO}_4\text{:K}_2\text{SO}_4$ ) is used as the stoichiometric oxidant but  $\text{H}_2\text{O}_2/\text{CH}_3\text{CN}$  can also be used (peroxyimide 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  $\text{K}_2\text{CO}_3$ ), 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  $\text{CH}_3\text{CN}$  (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  $\pi^*$  orbital of the olefin.



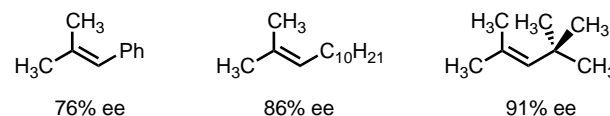
Higher ee's are observed with smaller  $\text{R}_1$  and larger  $\text{R}_3$  substituents.

## Examples:

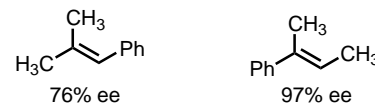
- Effect of smaller  $\text{R}_1$  (also: "T-branch"; phenyl groups can be considered smaller than methyl).



- Effect of larger  $\text{R}_3$  (also: "L-branch").

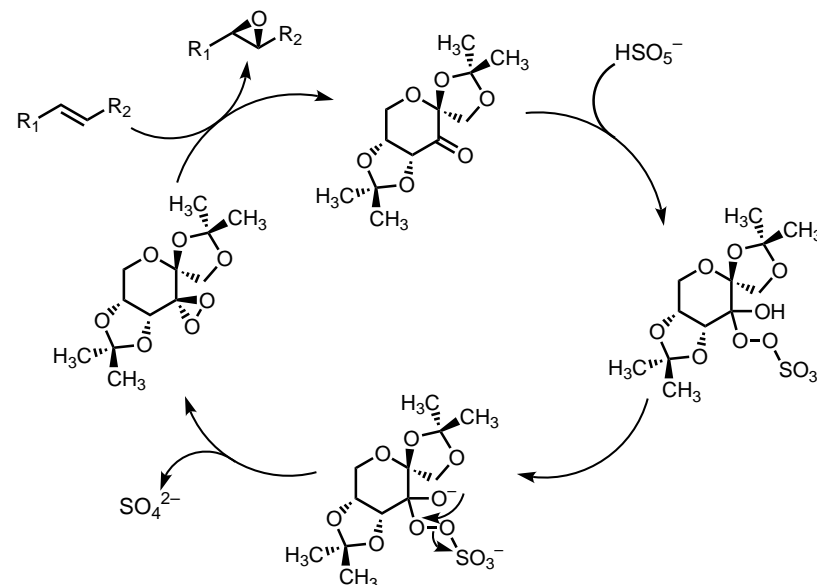


- Comparing the size of  $\text{R}_1$  and  $\text{R}_3$ .

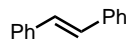

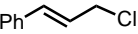

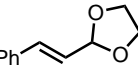
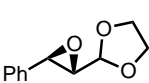
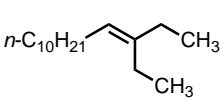
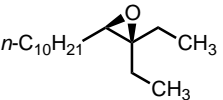


Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

## Proposed Catalytic Cycle:

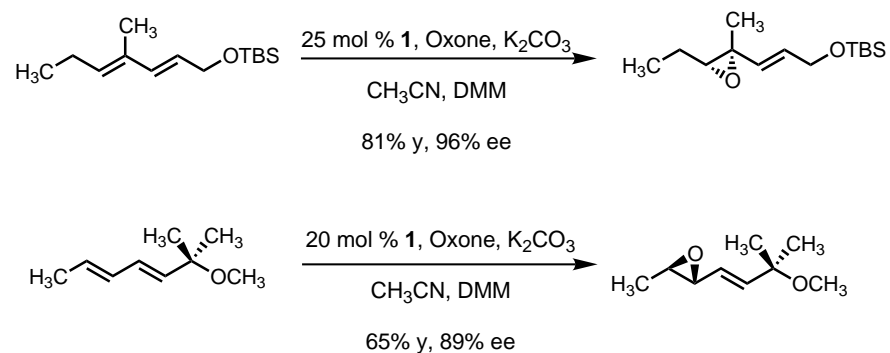


### Examples of Shi Epoxidations:

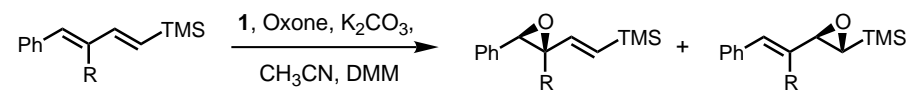
| Substrate   | Product   | Yield | ee (%) |
|---|---|-------|--------|
|  |  | 73%   | 95%    |
|  |  | 61%   | 93%    |
|  |  | 41%   | 93%    |
|  |  | 94%   | 89%    |

From: 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).



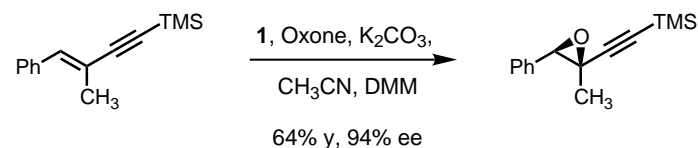
- Regioselectivity increases when either olefin of a 1,3-diene is trisubstituted. It is proposed that the trisubstituted olefin prevents full conjugation of the diene due to  $A_{1,2}$  strain, thereby isolating the olefins toward their individual steric or electronic environments.



|                     | Yield | ee  | Ratio |
|---------------------|-------|-----|-------|
| R = H               | 31%   | 95% | 1:1   |
| R = CH <sub>3</sub> | 77%   | 92% | 14:1  |

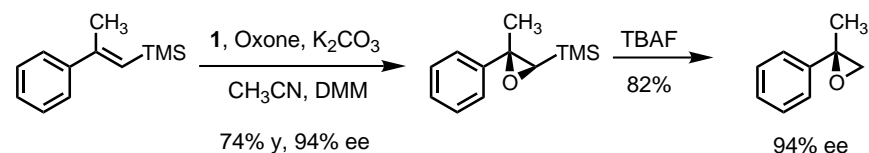
Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948-2953.

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



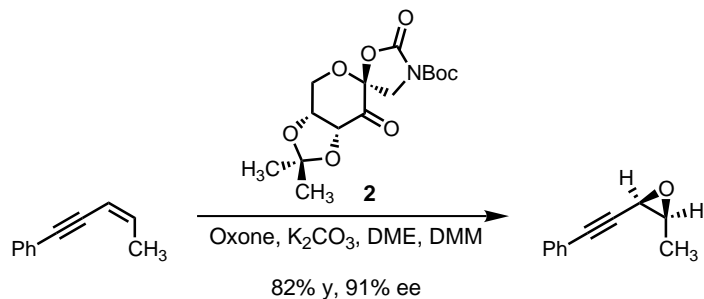
Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425-4428.  
Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646-7650.

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



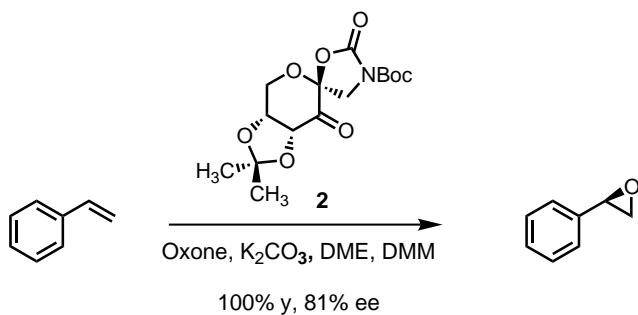
Warren, J.D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675-7677.

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



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

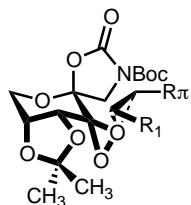
Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551-11552.



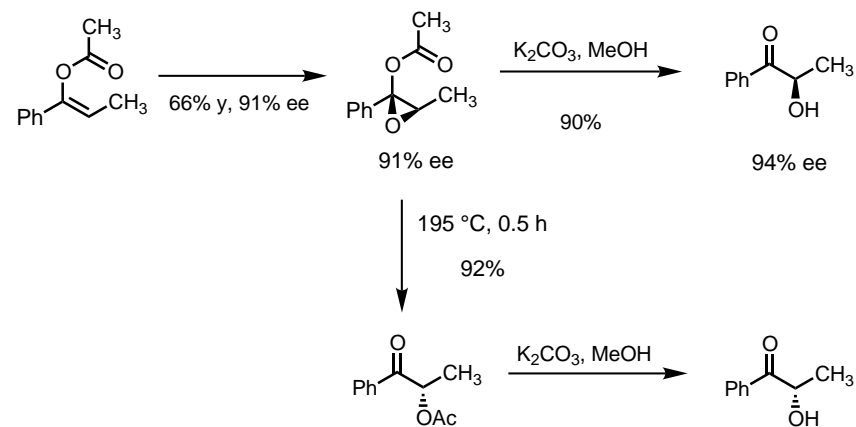
Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929-1931.

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  $\pi$ -substituent of the substituent prefers to be proximal to the spiro oxazolidinone.



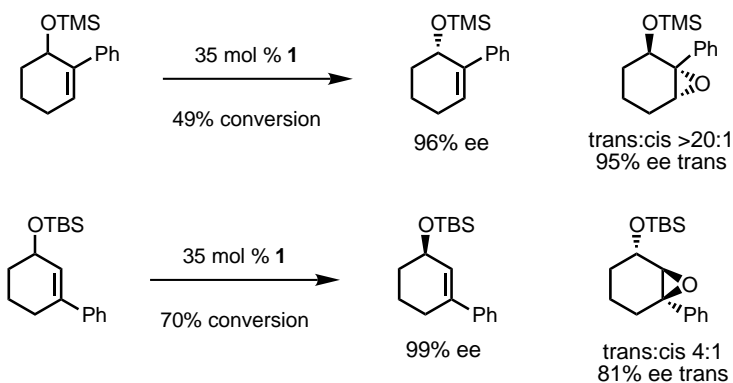
- Enol esters can be used as substrates for the preparation of  $\alpha$ -hydroxyketones in either enantiomeric form.



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

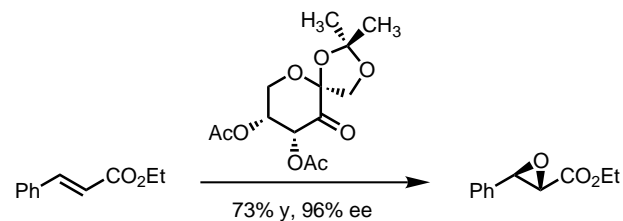
88% ee

- 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.

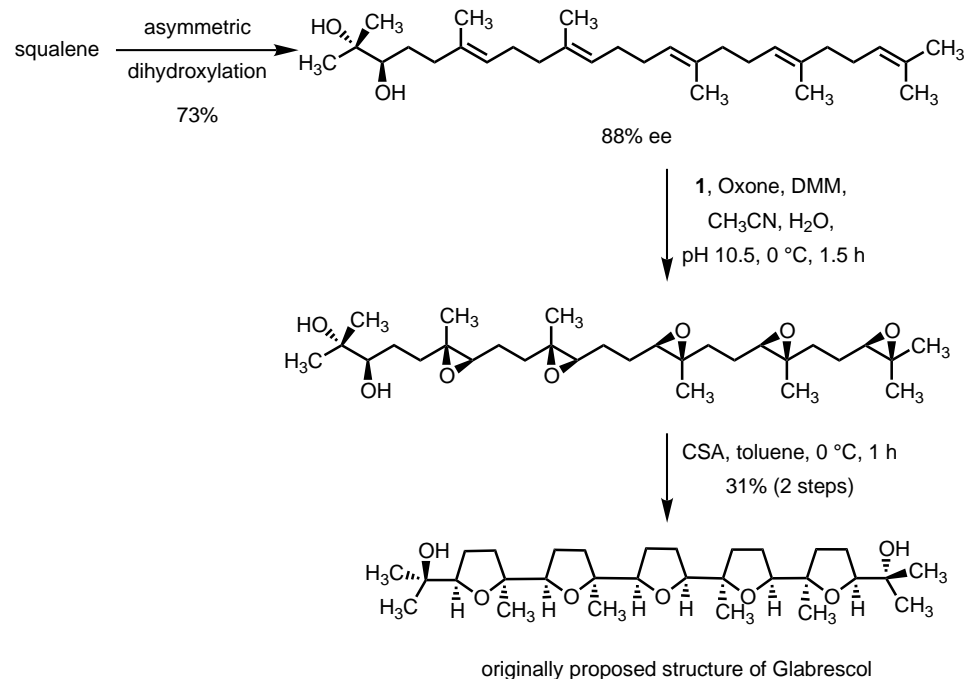
•The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient  $\alpha,\beta$ -unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.



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

### Applications in Synthesis:

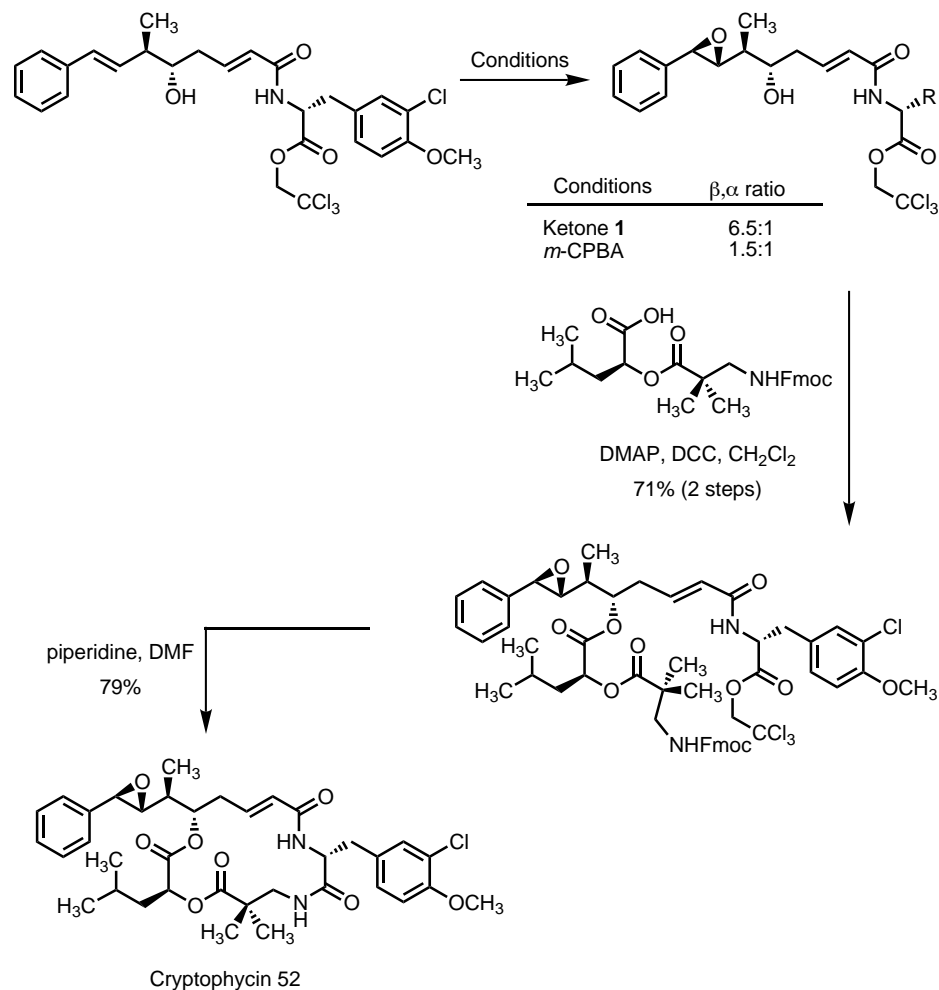
#### Glabrescol:



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

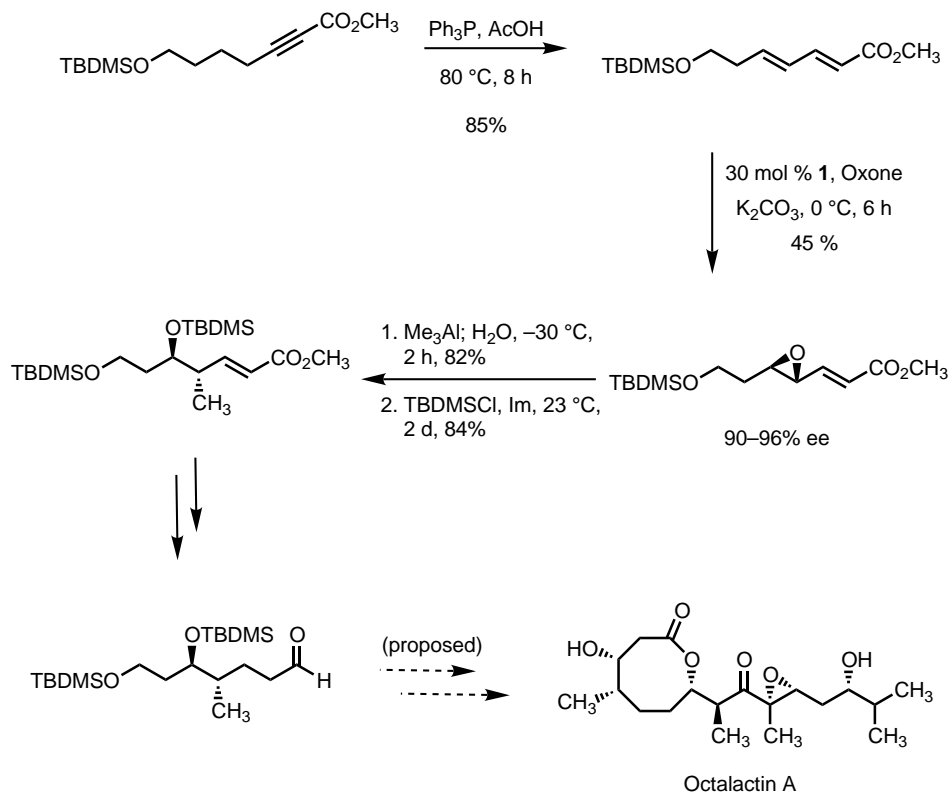
#### Cryptophycin 52:

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



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

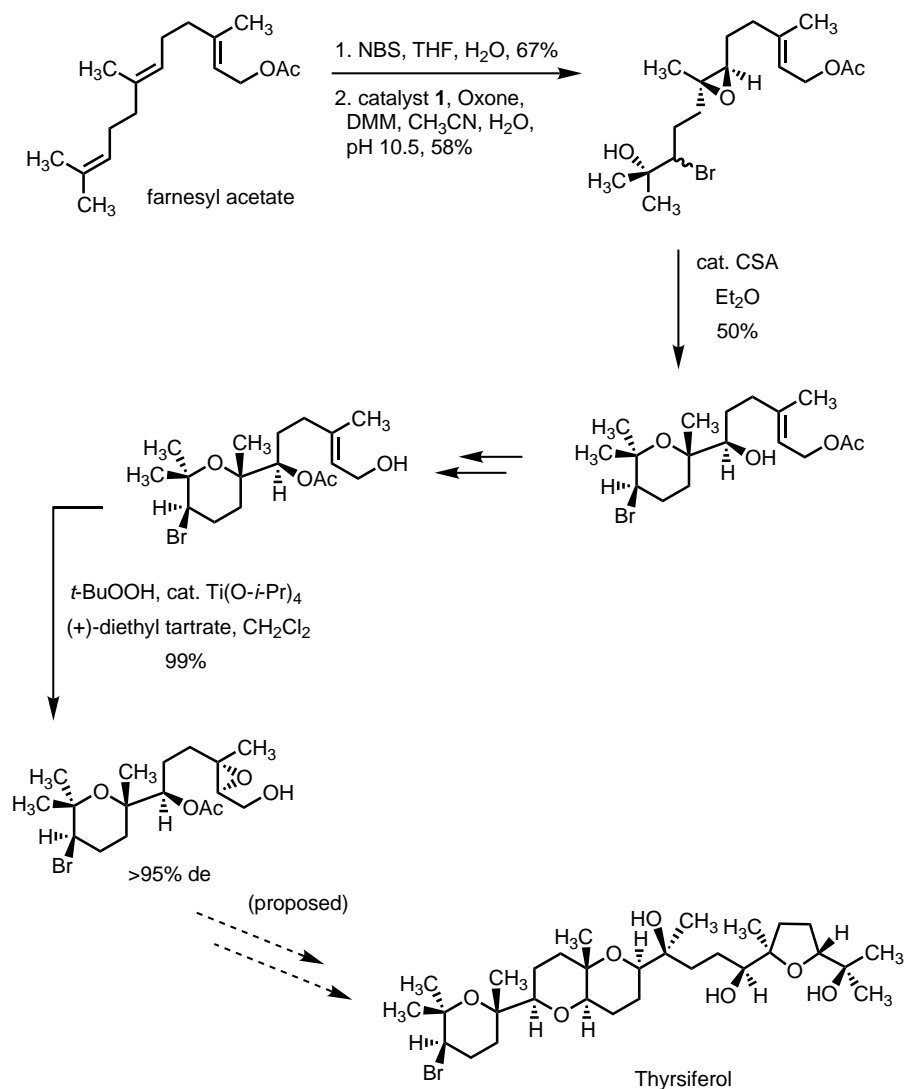
### Octalactin A:



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

### Thysiferol:

Effective kinetic resolution could be achieved in which only one bromotetrahydropyran diastereomer was formed in quantitative yield. The unreactive diastereomer was separated from the cyclization product and isolated in 30% yield.



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