

-Shikimic acid is a hydroaromatic intermediate in the common pathway of aromatic amino acid biosynthesis.

-First isolated in 1885 by Eykman from the fruit of *Illicium religiosum*. Found to exist widely in leaves of fruit of many plants and also in microorganisms, but in limited quantities.

-Relative and absolute stereochemistry realized only in 1930s through the works of Fischer, Freudenberg and Karrer.

-It is mainly involved in the biosynthetic shikimate pathway operative in plants and microorganisms and discovered by Davis, Sprinson and Gibson. Three amino acids (L-phenylalanine, L-tyrosine and L-tryptophan) are synthesized along the pathway.

-Available commercially (from Aldrich \$58.00 per gram). Limited availability from plants has led to the discovery of other synthetic and biosynthetic means to obtain shikimic acid. Recently reported to be derived from microbial fermentation of glucose using recombinant *E. coli*. Used as starting material for the synthesis of drug molecules and natural products.

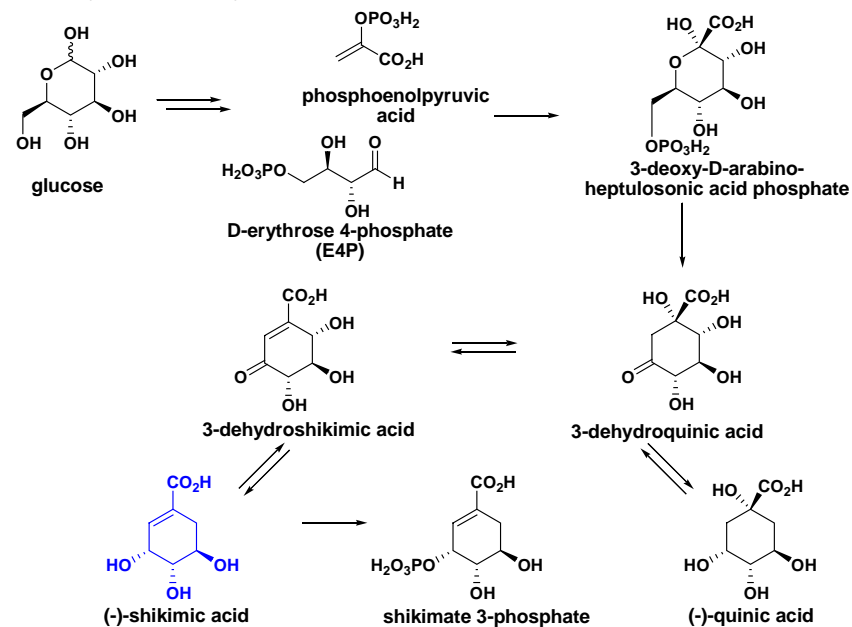
-There is great potential for the design and synthesis of enzyme inhibitors which may selectively block specific enzyme-catalysed transformations along this pathway.

References on recombinant microbial catalysis: 1) Draths, K. M.; Knop, D. R.; Frost, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 1603. 2) Knop, D. R.; Draths, K. M.; Chandran, S. S.; Barker, J. L.; von Daeniken, R.; Weber, W.; Frost, J. W. *J. Am. Chem. Soc.* **2001**, *123*, 10173. Leuenberger, H. G. W.; Matzinger, P. K.; Wirz, B. *Chimia* **1999**, *53*, 536.

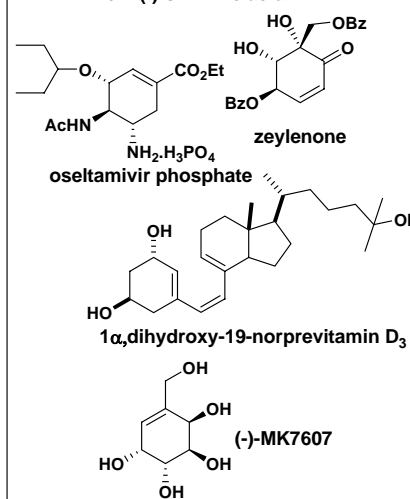
#### Reviews

- ii) Bohm, B. A. *Chem. Rev.* **1965**, *65*, 435.
- ii) Campbell, M. M.; Sainsbury, M.; Searle, P. A.. *Synthesis* **1993**, 179.
- iii) Jiang, S.; Singh, G. *Tetrahedron* **1998**, *54*, 4697.

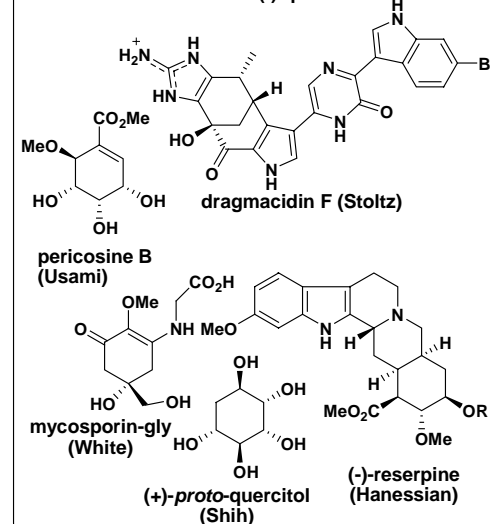
#### Biosynthetic pathway



#### Some molecules synthesized from (-)-shikimic acid



#### Some molecules synthesized from (-)-quinic acid

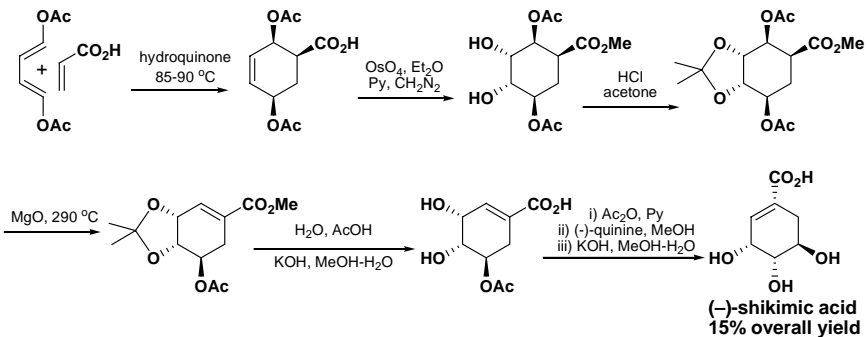


## SYNTHESIS OF SHIKIMIC ACID

- Several syntheses have been reported. The following discussion will cover some of them.

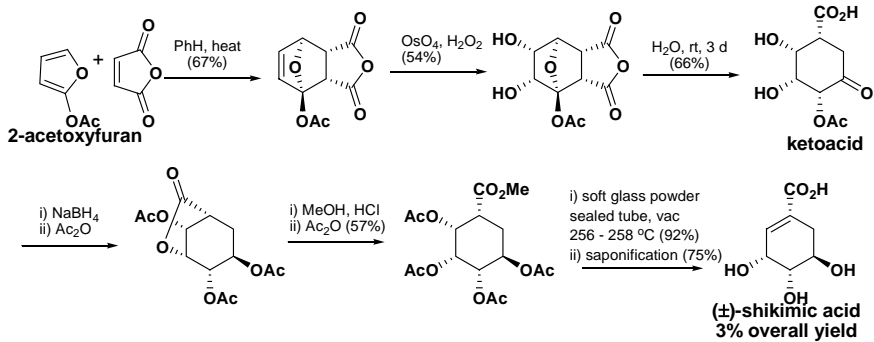
## Synthesis of shikimic acid via Diels Alder reaction

Raphael (1960) and Smissman (1959) - identical routes

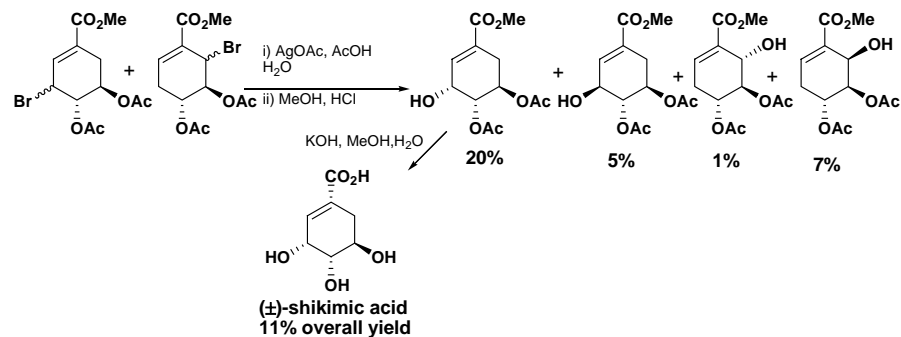
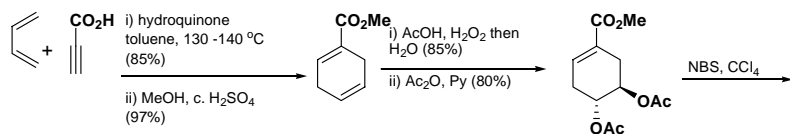


McCrindle, R.; Overton, K. H.; Raphael, R. A. *J. Chem. Soc.* **1960**, 1560.  
Smissman, E. E.; Suh, J. T.; Oxman, M.; Deniels, R. *J. Am. Chem. Soc.* **1959**, *81*, 2909.

## Smissman (1968)

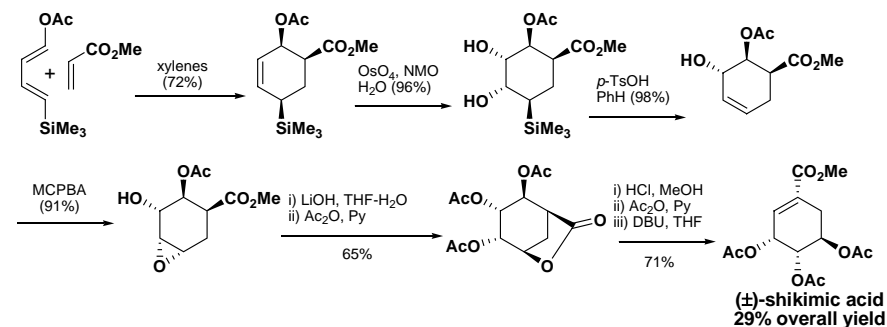


## Grewe (1964)

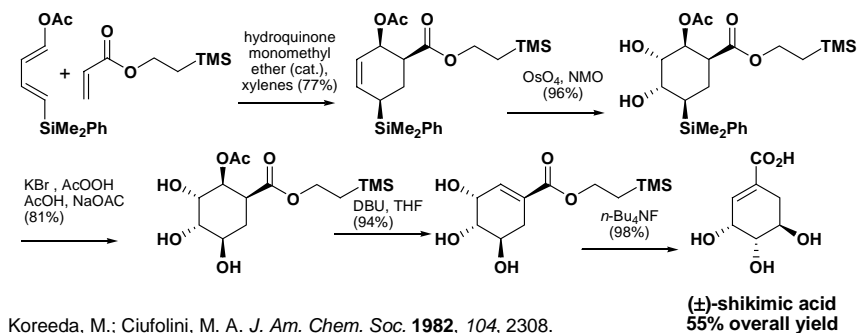


Grewe, R.; Hinrichs, I. *Chem. Ber.* **1964**, *97*, 443.

## Koreeda (1982)

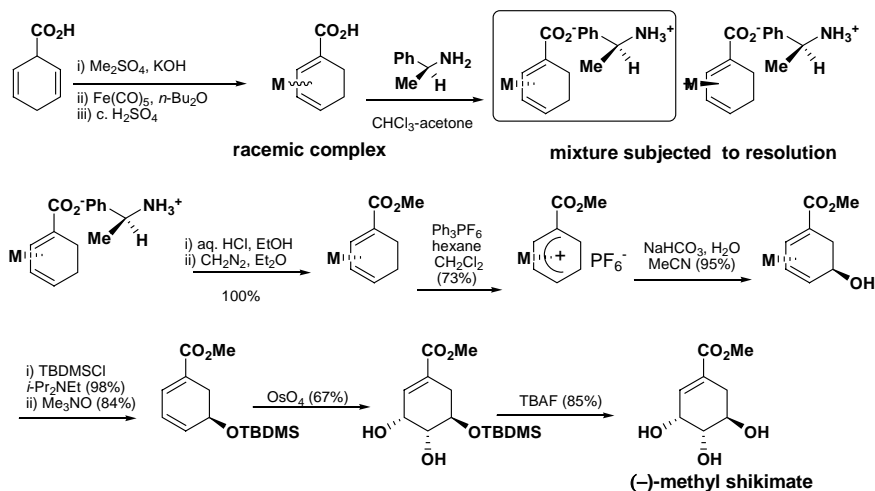


## Koreeda's 2nd generation synthesis employing Fleming oxidation

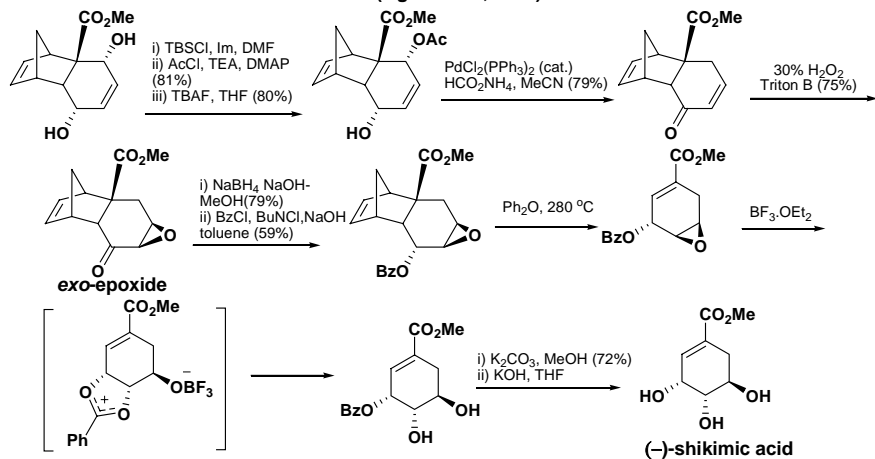


Koreeda, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 2308.  
Koreeda, M.; Teng, K.; Murata, T. *Tetrahedron Lett.* **1990**, *31*, 5997.

From benzene (Birch, 1988)

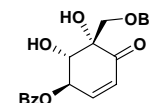
M =  $\text{Fe}(\text{CO})_3$ , provides lateral control for enantiospecifically installing the hydroxy groupBirch, A. J.; Kelly, L. F.; Weerasuria, D. V.; *J. Org. Chem.* **1988**, 53, 278.

Palladium mediated elimination reaction (Ogasawara, 2000)

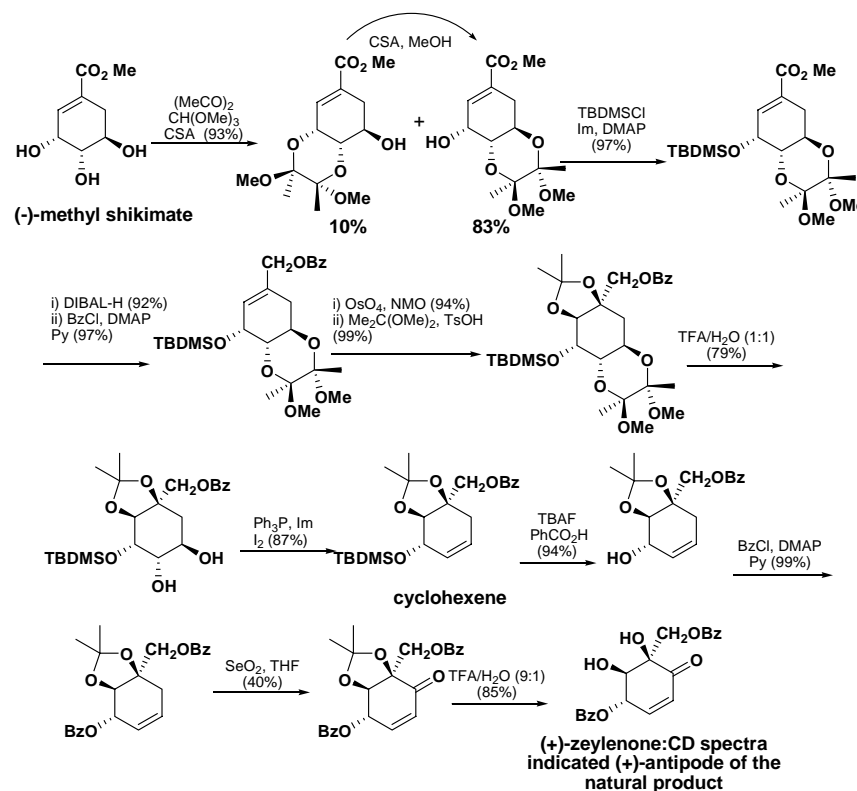
Yoshida, N.; Ogasawara, K. *Org. Lett.* **2000**, 2, 1461.

APPLICATIONS OF (-)-SHIKIMIC ACID IN SYNTHESIS

(-)-zeylonone

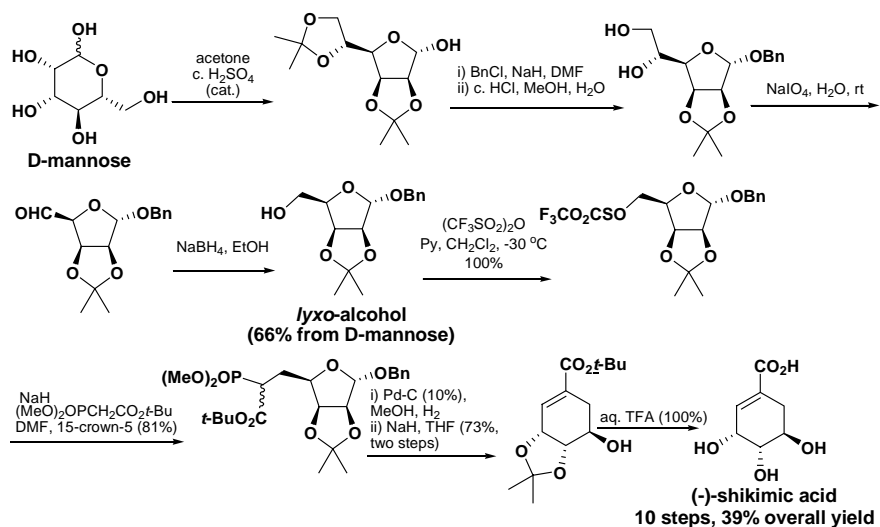
- a polyoxygenated cyclohexene showing antiviral, anticancer and antibiotic activities isolated from *Uvaria grandiflora*

Enantioselective synthesis of zeylonone from (-)-shikimic acid

Liu, A.; Liu, Z. Z.; Zou, Z. M.; Chen, S. Z.; Xu, L. Z.; Yang, S. L. *Tetrahedron*, **2004**, 60, 3689.

## Chiral syntheses of (-)-shikimic acid

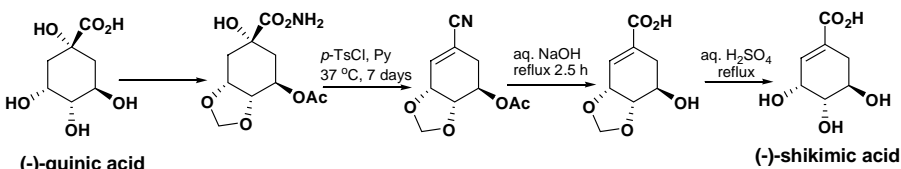
## From carbohydrates



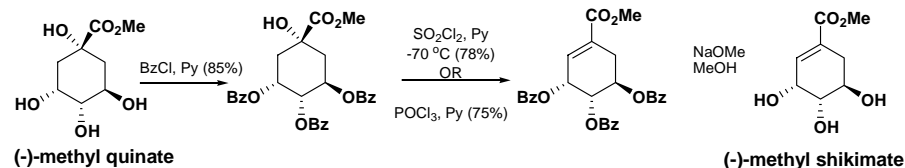
Fleet, G. W. J.; Shing, T. K. M.; Warr, S. M. *J. Chem. Soc. Perkin Trans. I*, **1984**, 905.

## From (-)-quinic acid

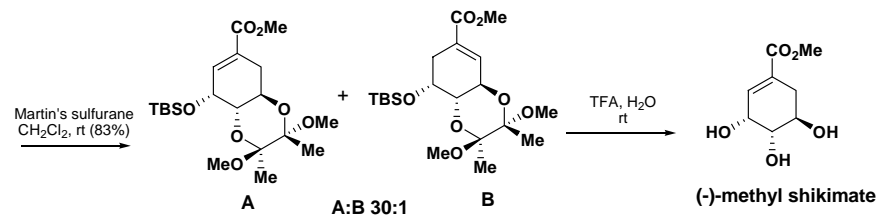
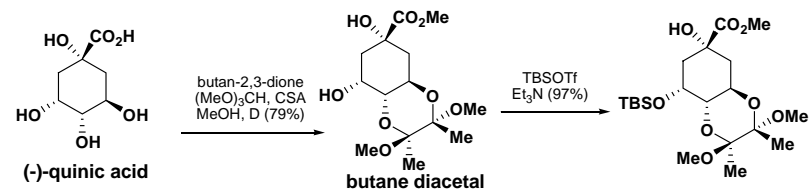
- several synthesis of (-)-shikimic acid from (-)-quinic acid have been published  
 - (-)-quinic acid is found in *Cinchona* bark and more readily available (available from Aldrich \$110.50 / 100g) than (-)-shikimic acid



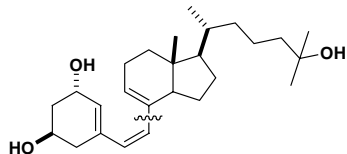
Dangschat, G.; Fischer, H. O. L. *Naturwissenschaften* **1938**, 26, 562. Dangschat, G.; Fischer, H. O. L. *Biochim. Biophys. Acta* **1950**, 4, 199.



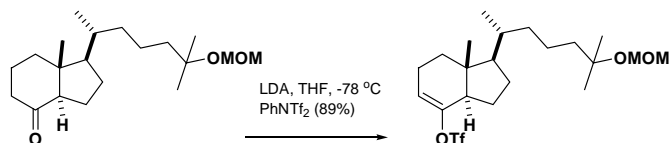
Cleophas, J.; Mercier, D.; Gero, S. D. *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 652.  
 Cleophas, J.; Leboul, J.; Mercier, D.; Gaudemer, A.; Gero, S. D. *Bull. Soc. Chim. Fr.* **1973**, 2992.



Box, J. M.; Harwood, L. M.; Humphreys, J. L.; Morris, G. A.; Redon, P. M.; Whitehead, R. C. *Synlett* **2002**, 2, 358.

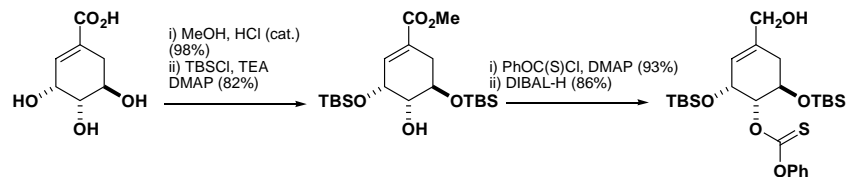
1 $\alpha$ ,dihydroxy-19-norprevitamin D<sub>3</sub>

- an analogue of the hormone 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>



known compound derived from  
vitamin D<sub>2</sub>

vinyl triflate



(-)-shikimic acid

*n*-Bu<sub>3</sub>SnH  
AIBN (cat.)  
(63%)

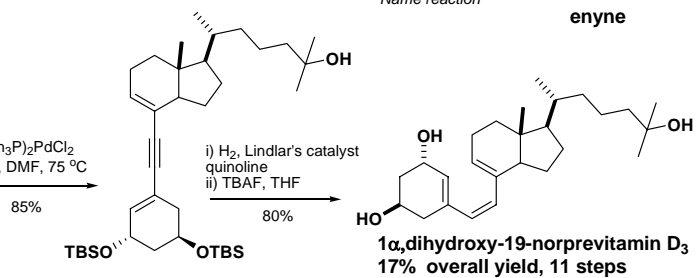
Name reaction

Name reaction

enyne

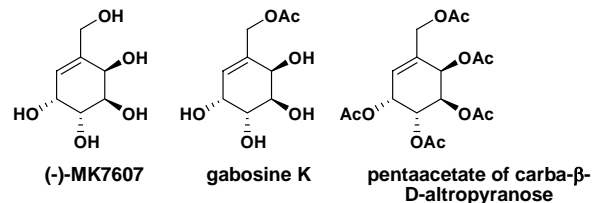
vinyl triflate

enyne

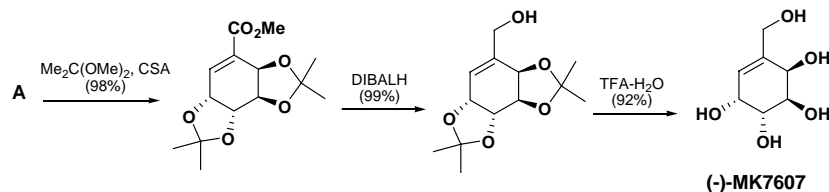
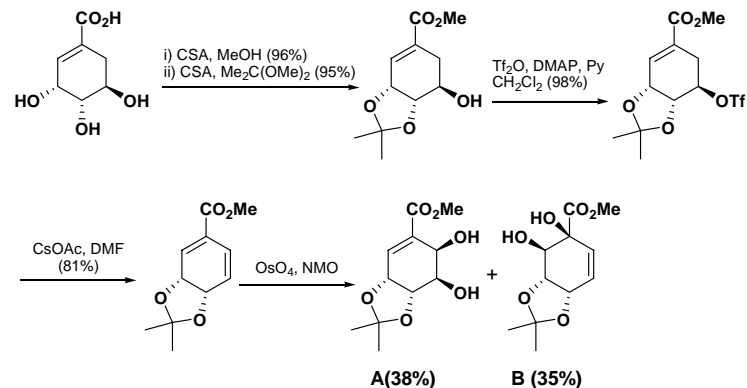


1 $\alpha$ ,dihydroxy-19-norprevitamin D<sub>3</sub>  
17% overall yield, 11 steps

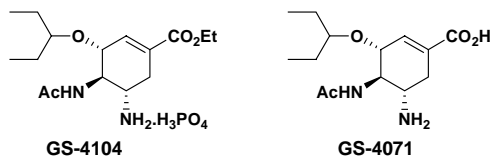
## Synthesis of (-)-MK7607 and other carbasugars



- carbasugars or pseudosugars lack the acetal function which is characteristic of common monosaccharades  
- known to display a range of biological activities, particular as glycosidase inhibitors

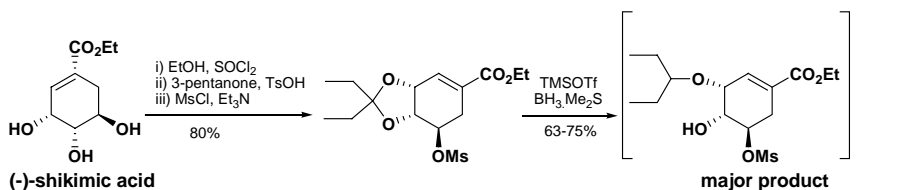


## Kilogram scale synthesis of Oseltamivir phosphate (Tamiflu)

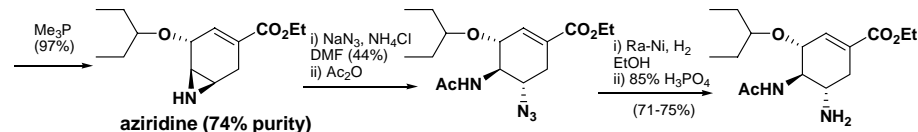
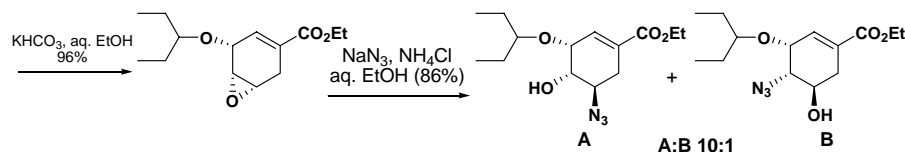


-it is a prodrug of the potent and selective competitive inhibitor (GS-4071) of influenza A and B neuraminidase

-research and development by Gilead Sciences Inc. and F. Hoffmann-La Roche Ltd.

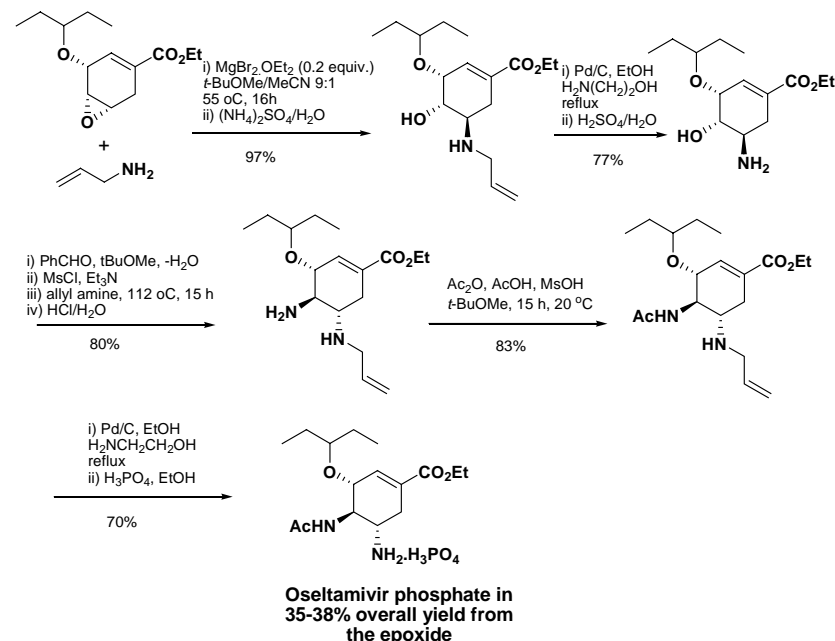


(-)-shikimic acid



21% overall yield in 10 steps from (-)-shikimic acid

## Roche-Basel Route to oseltamivir phosphate (azide free synthesis)



Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044.

- Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.
- Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Shultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545.

## Industrial synthesis of oseltimivir phosphate (50-250 kg)

