Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route

Tsuyoshi Mita, Nobuhisa Fukuda, Francesc X. Roca, Motomu Kanai,* and Masakatsu Shibasaki*

Org. Lett. 2007, ASAP

Presented by: Edmund Yeh
Jan. 8th 2007

Outline

- Background information
- Previous synthesis and their limitations
- Improved synthesis form Shibasaki
- Conclusion

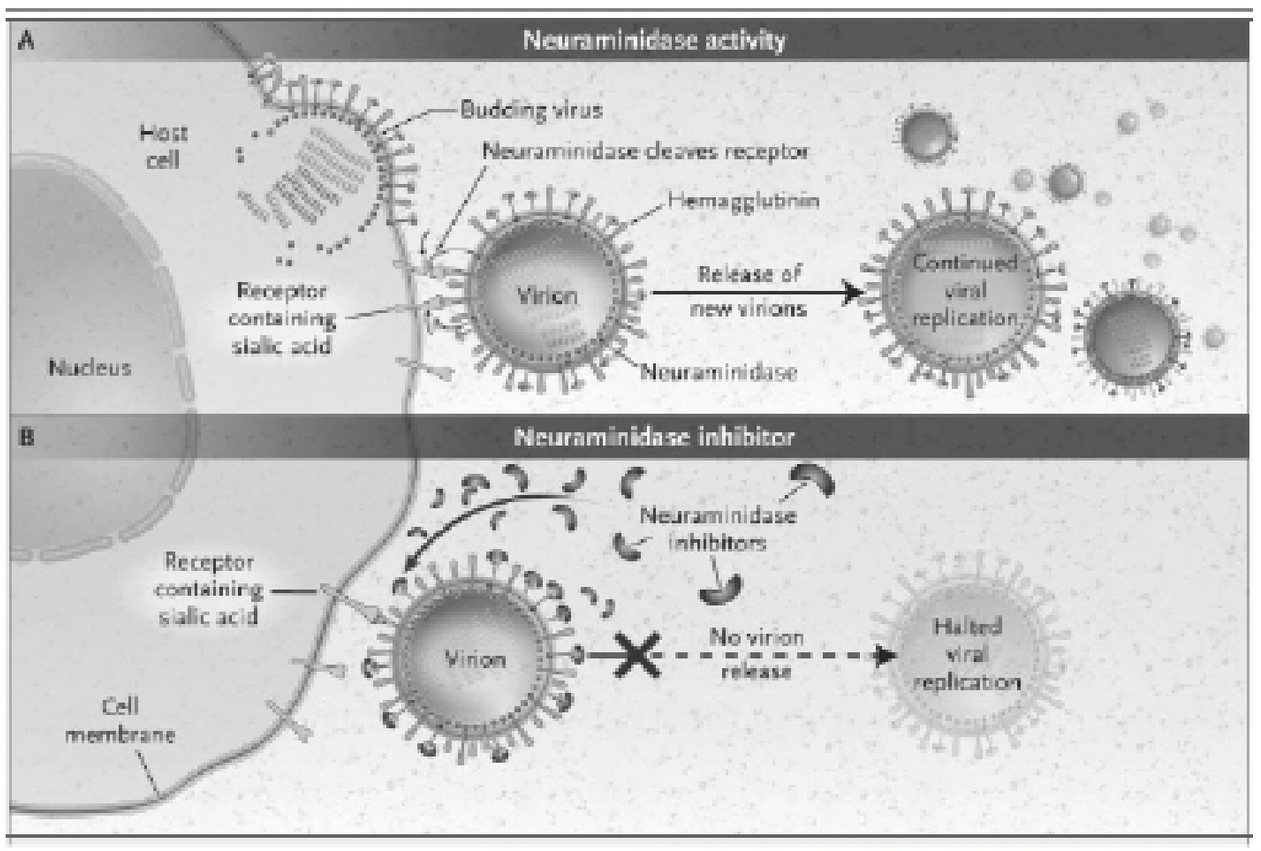
Current Treatments for Influenza

- There are two classes of drugs currently used as treatment for influenza (flu).
  - Adamantanes: amantadine and rimantadine
  - Neuraminidase Inhibitors: zanamivir and oseltamivir
- Avian influenza is resistant to adamantane drugs

- Oseltamivir phosphate (Tamiflu™) was found to be the only effective treatment for avian influenza virus (H5N1)

Moscona A. *N. Engl. J. Med.* **2005**, 353, 13, 1363

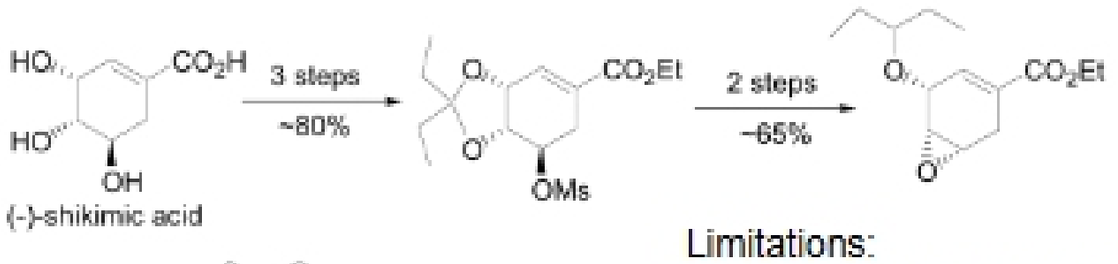
Neuraminidase Inhibitor

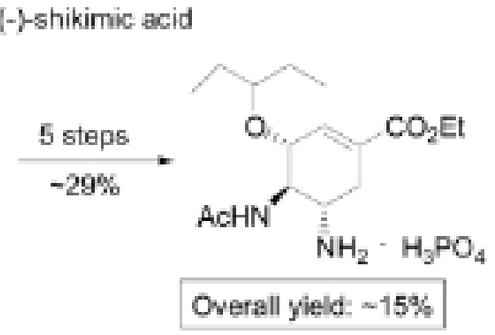


Moscona A. *N. Engl. J. Med.* **2005**, 353, 13, 1363

Previous Synthesis of Tamiflu™

- Karpf *et al.* synthesis used (-)-quinic acid or (-)-shikimic acid as starting material.





Overall yield: ~15%

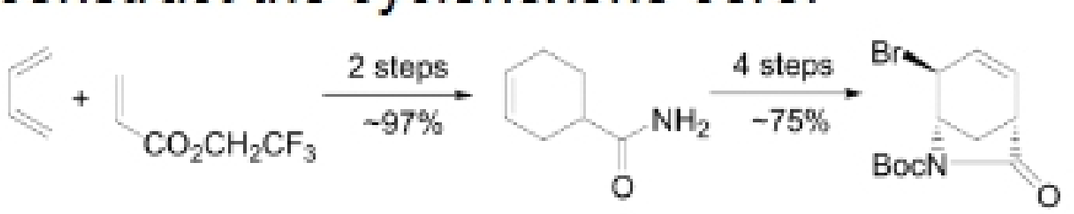
Limitations:
1. Starting materials are expensive.
2. Use of azide to open up epoxide is potentially hazardous.

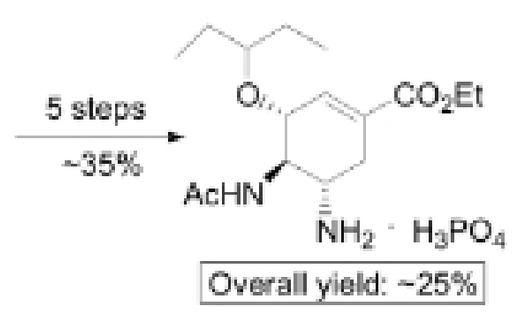
Rohloff, J. *et al. J. Org. Chem.* **1998**, 63, 4545

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

Previous Synthesis of Tamiflu™

- Corey *et al.* used Diels-Alder reaction to construct the cyclohexene core.





Overall yield: ~25%

Limitations:
1. Some of the transformation requires low temperature conditions.
2. Some reagents used could be hard to scale up, i.e. CCl_4.

Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. am. Chem. Soc.* **2006**, 128, 6310