Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route

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

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Presented by: Edmund Yeh
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Outline

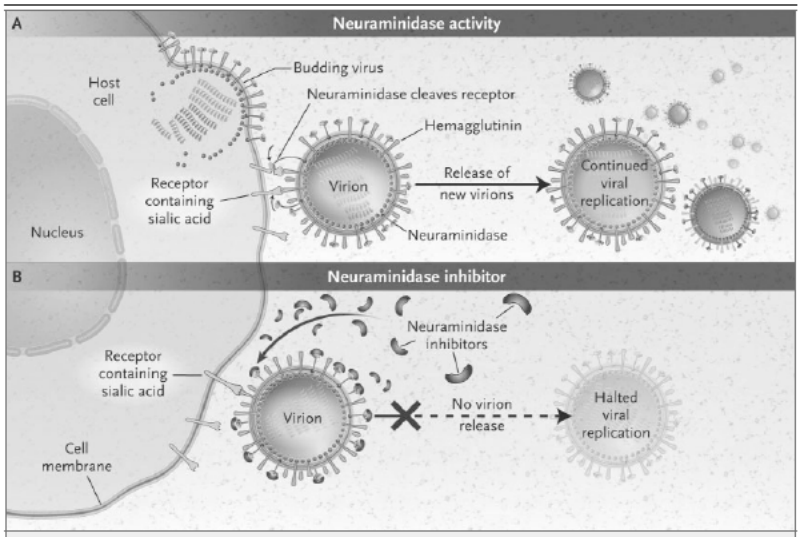
- Background information
- Previous synthesis and their limitations
- Improved synthesis form Shibasaki
- Conclusion

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^{TM}) was found to be the only effective treatment for avian influenza virus (H5N1)

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

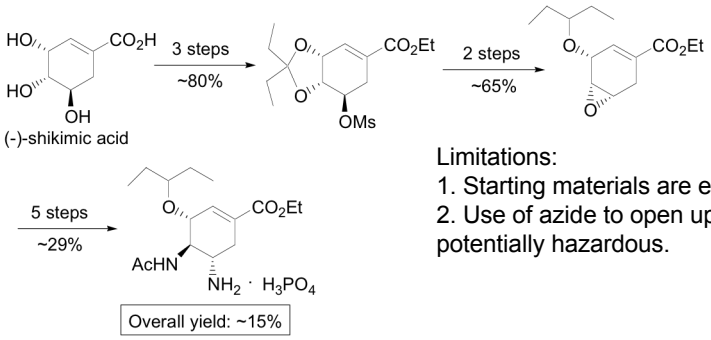
Neuraminidase Inhibitor



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.



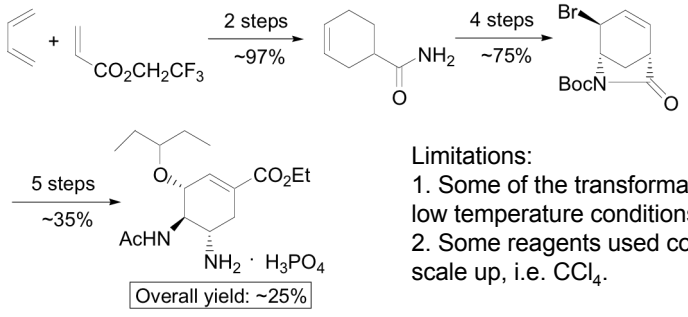
Limitations:
1. Starting materials are expensive.
2. Use of azide to open up epoxide is potentially hazardous.

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.

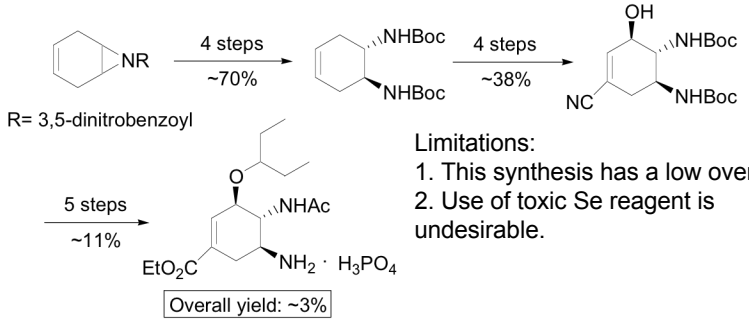


Limitations:
1. Some of the transformation requires low temperature conditions.
2. Some reagents used could be hard to scale up, i.e. CCl_4.

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

Previous Synthesis of Tamiflu™

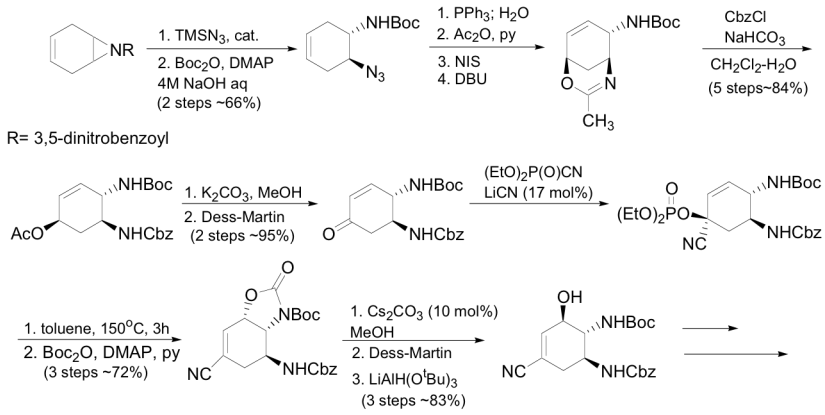
- Shibasaki *et al.* showcased his catalytic asymmetric ring opening of meso-aziridine.



Limitations:
1. This synthesis has a low overall yield.
2. Use of toxic Se reagent is undesirable.

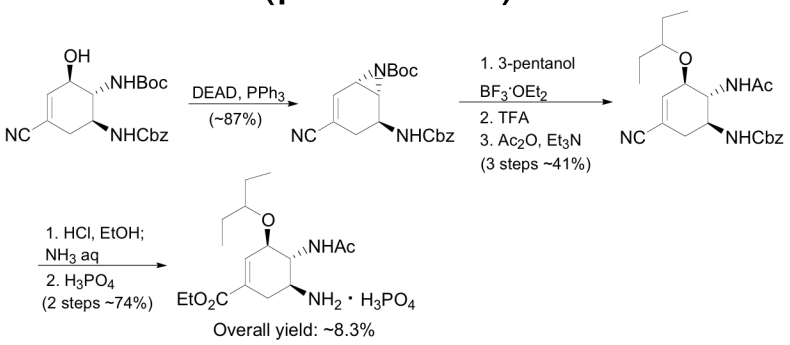
Shibasaki, M. *et al. J. am. Chem. Soc.* **2006**, 128, 6312

M. Shibasaki Tamiflu™ Synthesis (part deux)



Shibasaki, M. *et al. Org. Lett.* **2007**, ASAP

M. Shibasaki Tamiflu™ Synthesis (part deux)



Overall yield: ~8.3%

Shibasaki, M. *et al. Org. Lett.* **2007**, ASAP

Conclusion

- Shibasaki presented an alternative way of Tamiflu™ synthesis.
- SeO_2 allylic oxidation step from first paper was replaced by non-toxic transformations.
- Overall yield improved dramatically but still not as high as current method.
- New ways of obtaining (-)-shikimic acid has been found and will be mass produced soon.