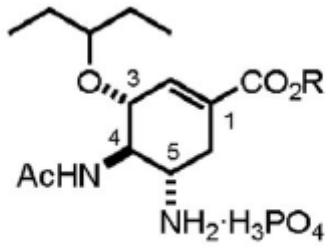
Synthesis of the Anti-influenza Drug

Oseltamivir Phosphate (Tamiflu®)



6: oseltamivir phosphate (R = Et)

Marie-Alice Virolleaud

Bibliography – October the 28th 2008

Needs in new influenza virus drug

Historical influenza pandemics or epidemics in the 20th century:

- 1918 Spanish flu (between 20 and 40 million people killed, more than during 1st world war)
- 1957 Asian flu
- 1968 Honk Kong flu

All three were caused by recombinant virus (reassortment between human viruses and bird viruses)

- 1997 Hong Kong: avian H5N1 influenza apparition
  H5N1 virus infected over 100 persons, lethality rate is over 50%
  This virus is purely avian, it does not spread from human to human

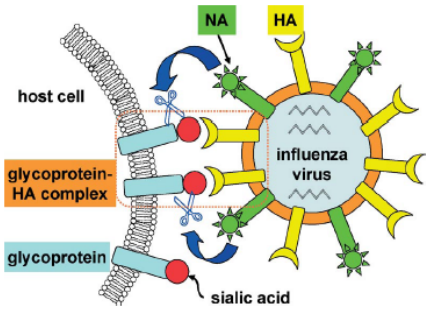
In the next future, mutated form of this virus might lead to a new influenza pandemic

Hypothesis: structures of fundamental proteins are conserved even in mutant viruses
So a well-designed inhibitor of one of these fundamental proteins might become an efficient drug / weapon against the threat of a new influenza epidemic.

Needs in new influenza virus protein inhibitors

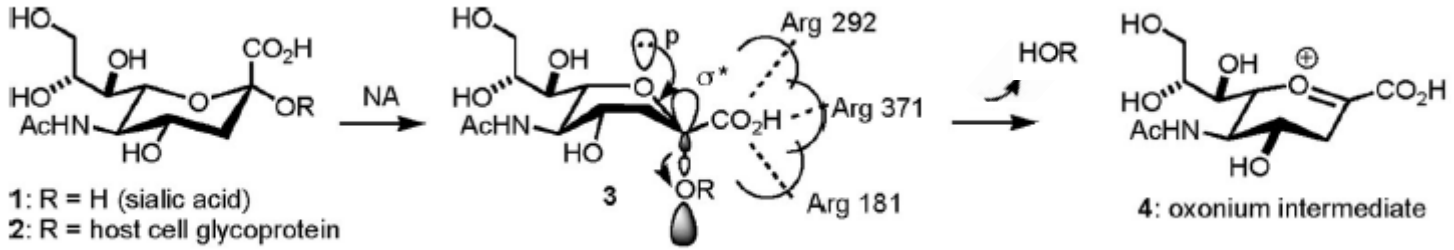
Political worldwide concern:
how under-developed countries will be able to stock drugs in prevision of this hypothetical pandemic?

Neuraminidase inhibitors:
Oseltamivir phosphate design



Schematic representation of neuraminidase action

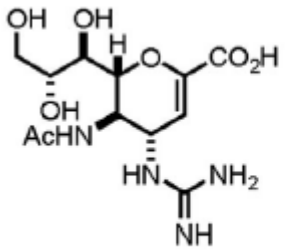
Hydrolysis step of sialic acid by neuraminidase (NA)



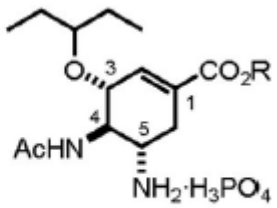
Design of neuraminidase inhibitors by transition state mimic:

Zanamivir (Relenza):
low bioavailability, administered by inhalation

Oseltamivir phosphate (Tamiflu):
orally active prodrug
active form is corresponding carboxylic acid

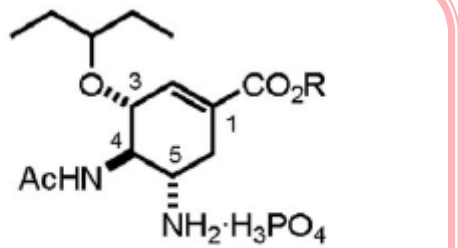


5: zanamivir



6: oseltamivir phosphate (R = Et)

Oseltamivir Phosphate (Tamiflu®)



6: oseltamivir phosphate (R = Et)

- Description

  Cyclohexene core, 3 stereogene carbons (3*R*, 4*R*, 5*S* / *anti*, *anti*)
  Functionalities: 1 conjugated ester, 1 alkyloxy moiety, 2 nitrogen moieties

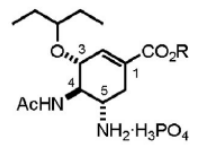
- Chronology

  1997: Tamiflu is created by Gilead Science
  1997-1998: co-development by Gilead Science and Roche
  2006: beginning of academic syntheses
  Corey, Shibasaki and Kanai, Yao
  2007: Fukuyama, Kann, Fang
  2008: Trost

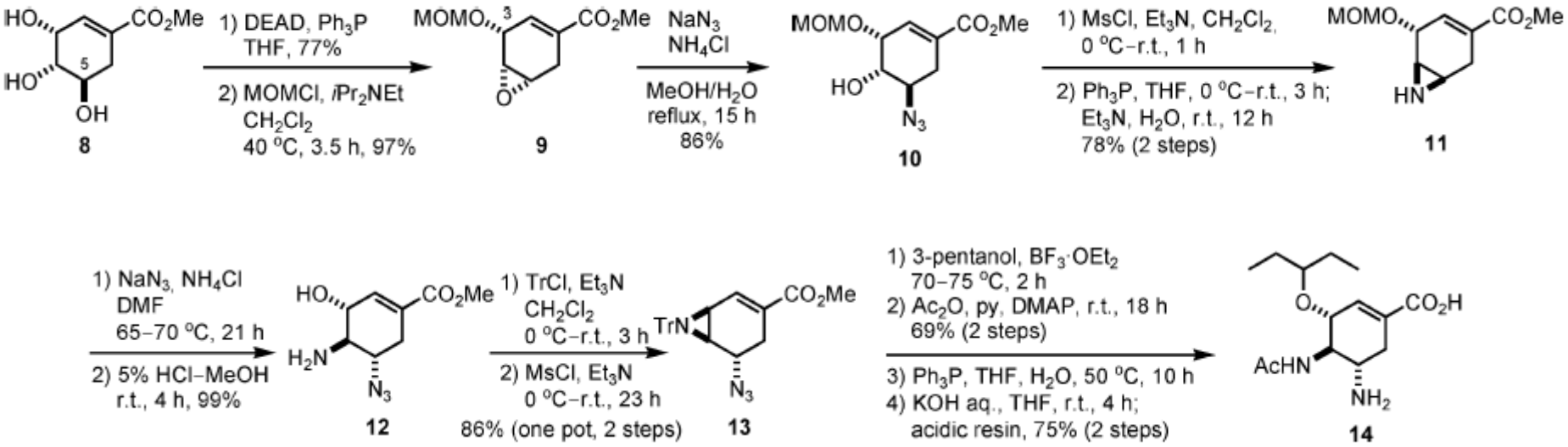
- 2 reviews

  Tamiflu: The Supply Problem
  Farina, V.; Brown, J. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 7330–7334.
  Synthetic Strategies for Oseltamivir Phosphate
  Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839-1850.

Gilead Sciences synthesis



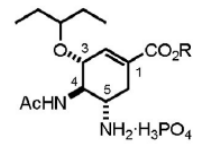
6: oseltamivir phosphate (R = Et)



- 15 steps, ~21% (formally, from shikimic acid)
- Starting material: shikimic acid derivative (ester)
- *Trans* 1,2-diamine introduction : iterative aziridine opening with azide
- Pentyloxy introduced at the latest stage of the synthesis (analogues might be easily obtained)

(a) 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, W. G.; Stevens R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681-690. (b) 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.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998,** *63,* 4545-4550

Roche industrial synthesis (1/2)

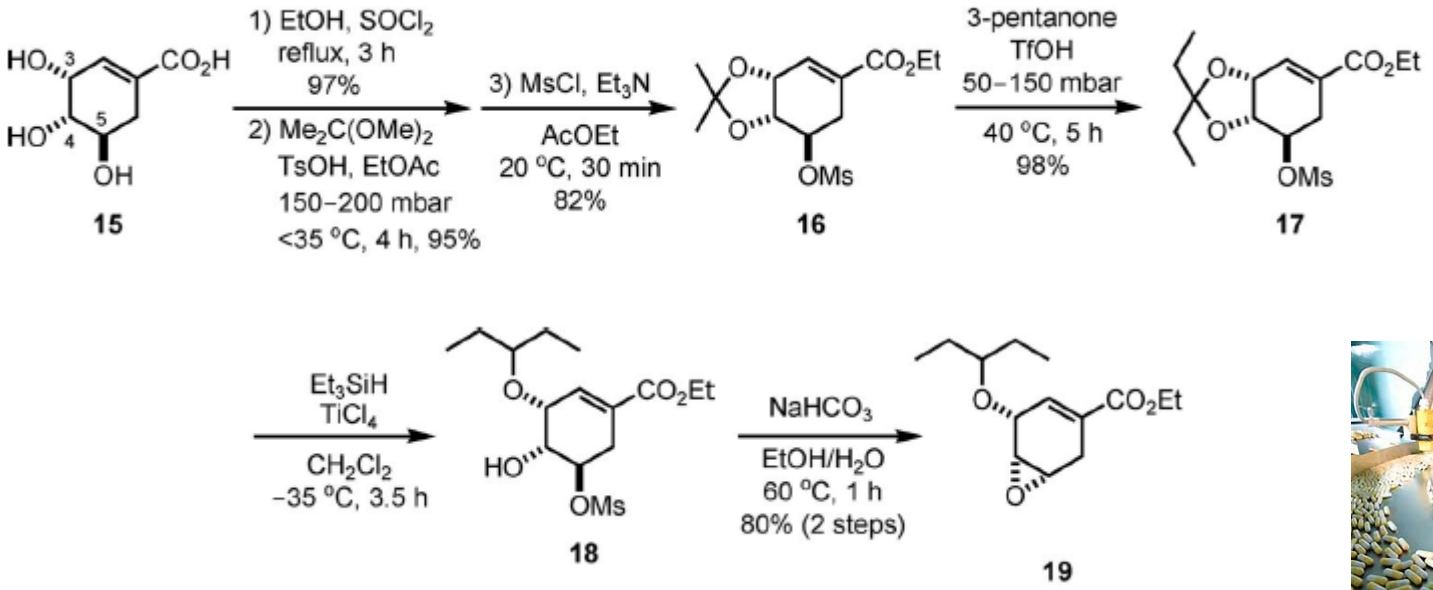


6: oseltamivir phosphate (R = Et)

- Shikimic acid as starting material: two drawbacks

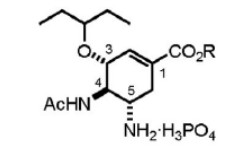
  Availability of starting material in large scale. Shikimic acid is extracted from Chinese star anise. 1kg is obtained from 30kg of dried plants.

  Purity of the starting material is variable (85 to 99%)

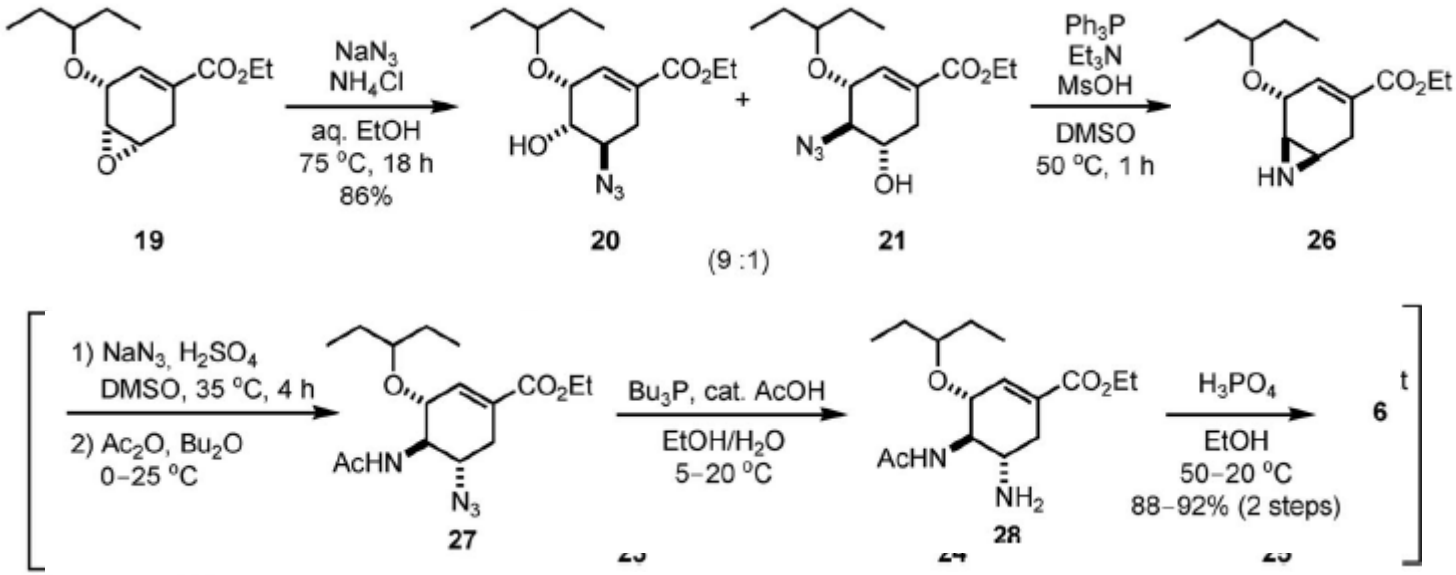


Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen A. G. *Org. Process Res. Dev.* **1999**, *3*, 266–274.

Roche industrial synthesis (2/2)



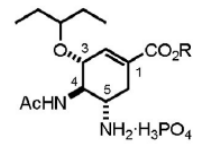
6: oseltamivir phosphate (R = Et)



- 12 steps, ~30%
- Drawbacks
  - (1) starting material (as mentioned above)
  - (2) use of potentially explosive azide-containing intermediates

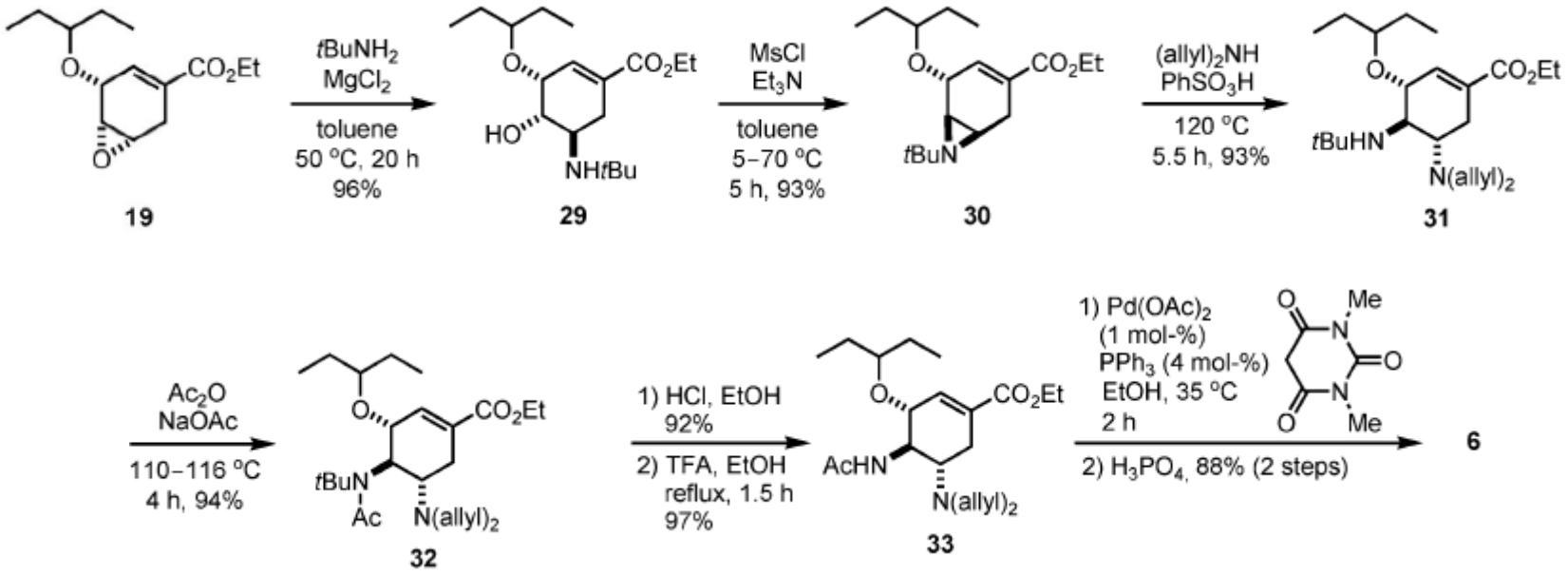
Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen A. G. *Org. Process Res. Dev.* **1999**, *3*, 266–274.

Roche synthesis
without azide as source of nitrogen



6: oseltamivir phosphate (R = Et)

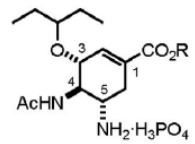
Alternative sources of amine: *t*BuNH$_2$ and (allyl)$_2$NH



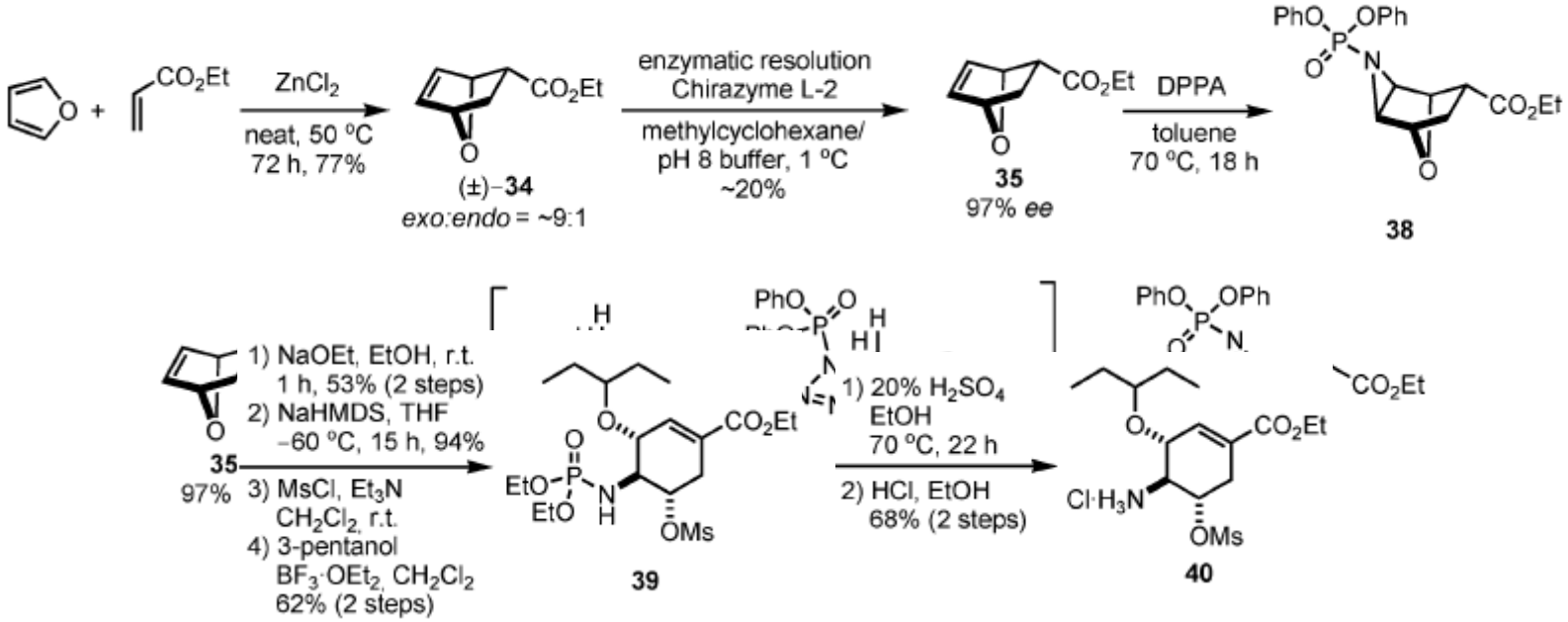
- only one purification for the sequence (compound 32 by precipitation)
- 14 steps (12 with azides)

Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86–91.
Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044–2051.

Roche : Diels-Alder strategy

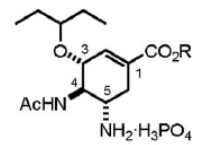


6: oseltamivir phosphate (R = Et)

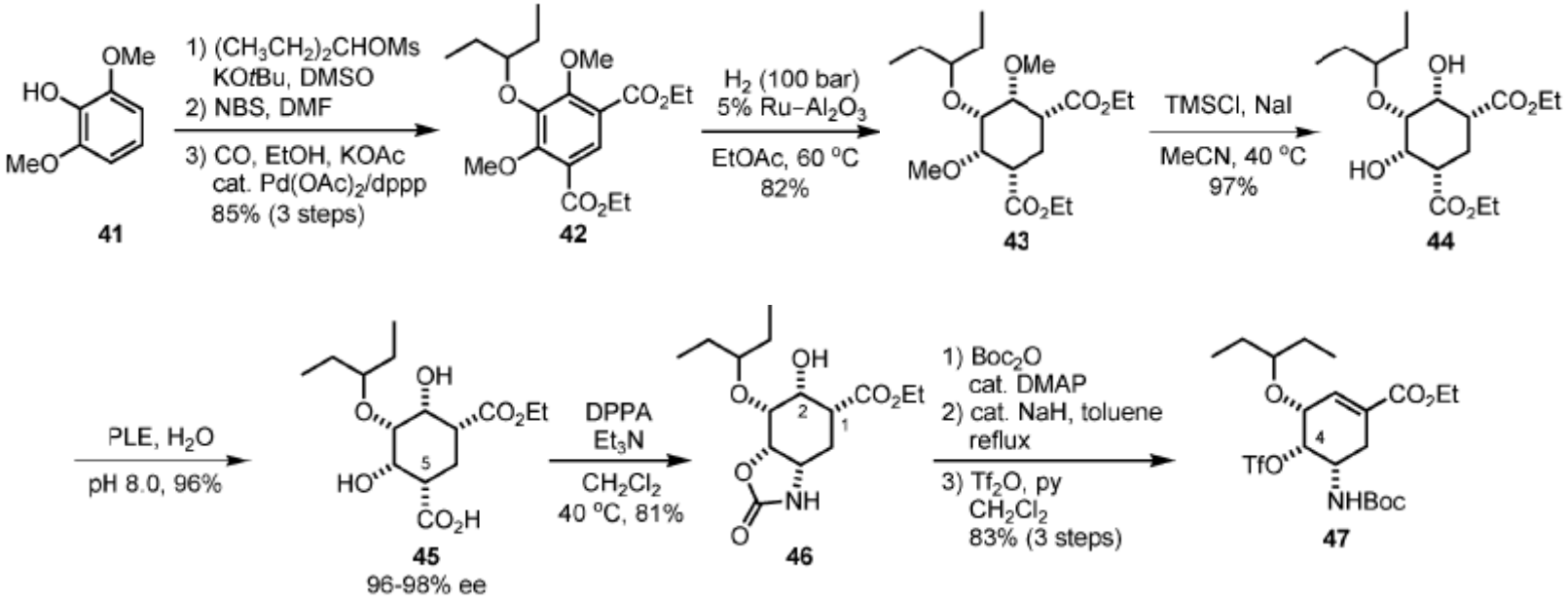


- starting material: furane and ethyl acrylate
- key steps: racemic Diels-Alder, [3+2] cycloaddition with DPPA (= diphenylphosphoryl azide)
- major drawback, yield of the resolution: ~20%
- Origin of the chirality: enzymatic resolution

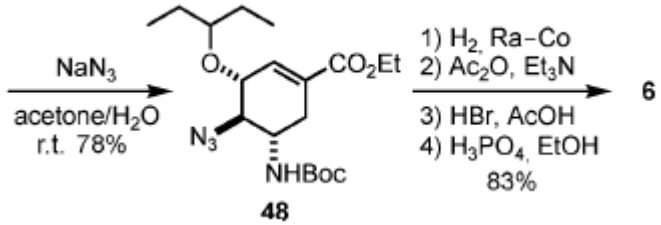
Roche : desymmetrization strategy



6: oseltamivir phosphate (R = Et)

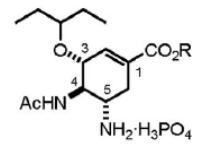


- 15 steps, ~30%
- starting material 1,6-dimethoxyphenol
- key steps: cis hydrogenation, Curtius rearrangement
- origin of the chirality: enzymatic desymmetrization



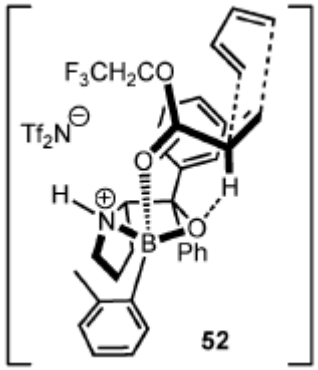
Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895-4902.

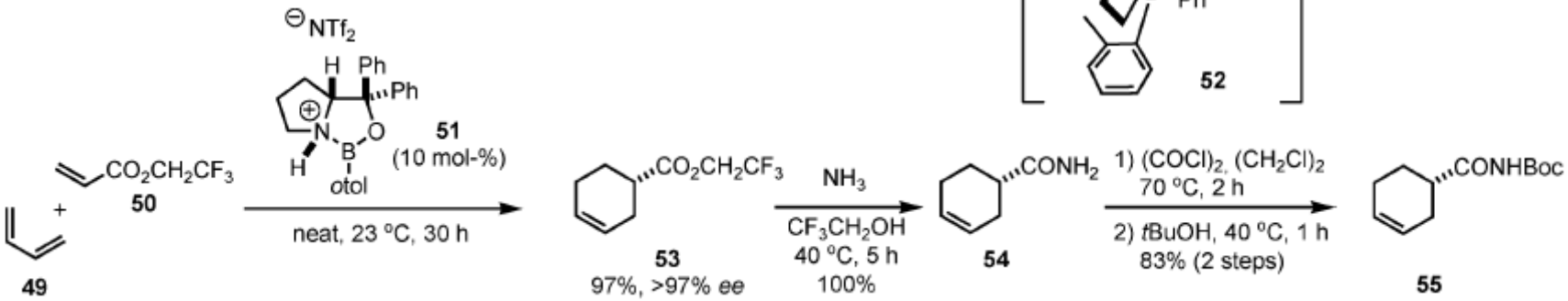
Corey synthesis (1/2)

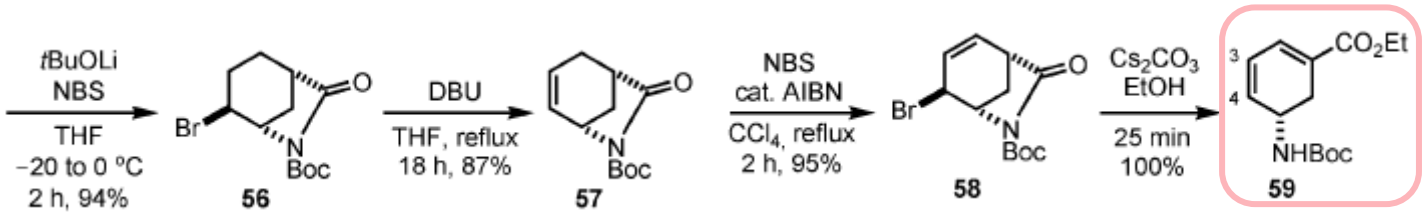


6: oseltamivir phosphate (R = Et)

Synthesis based on an enantioselective Diels-Alder reaction





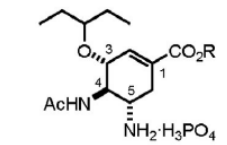


Corey's intermediate

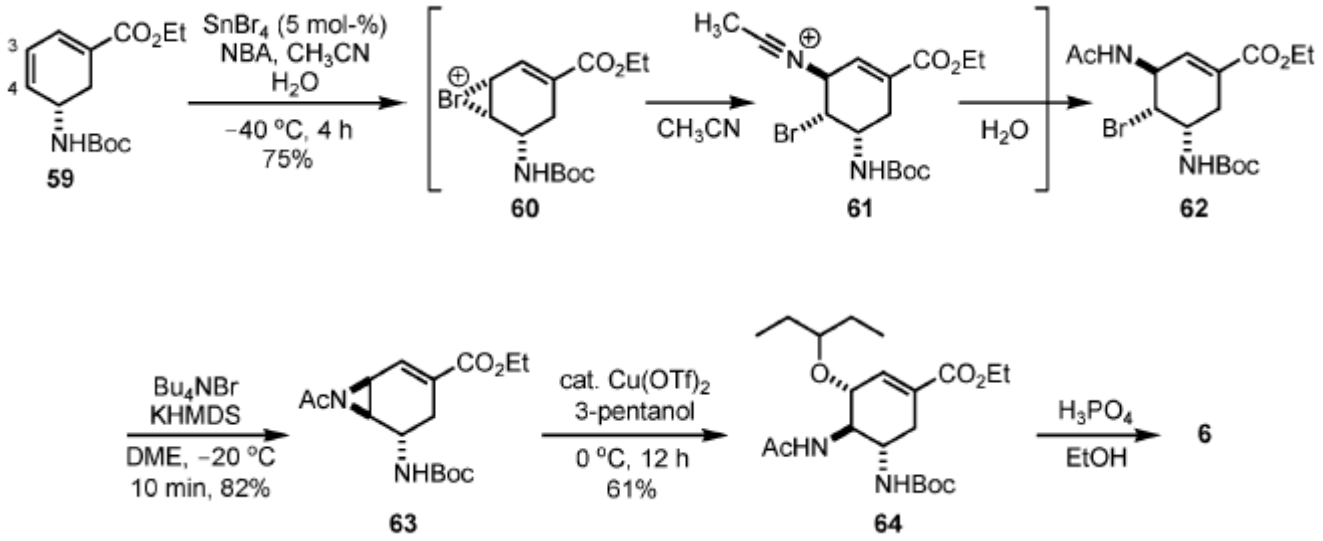
8 steps to reach diene 59

Yeung, Y.-Y.; Hong, S.; Corey, E. J.; *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.

Corey synthesis (2/2)



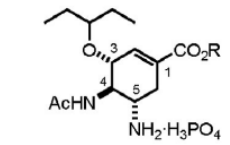
6: oseltamivir phosphate (R = Et)



- 12 steps, ~30%
- starting material: 1,3-butadiene and trifluoroethyl acrylate
- key steps: Diels-Alder reaction, stereoselective bromoamidation
- origin of the chirality: enantioselective Diels-Alder

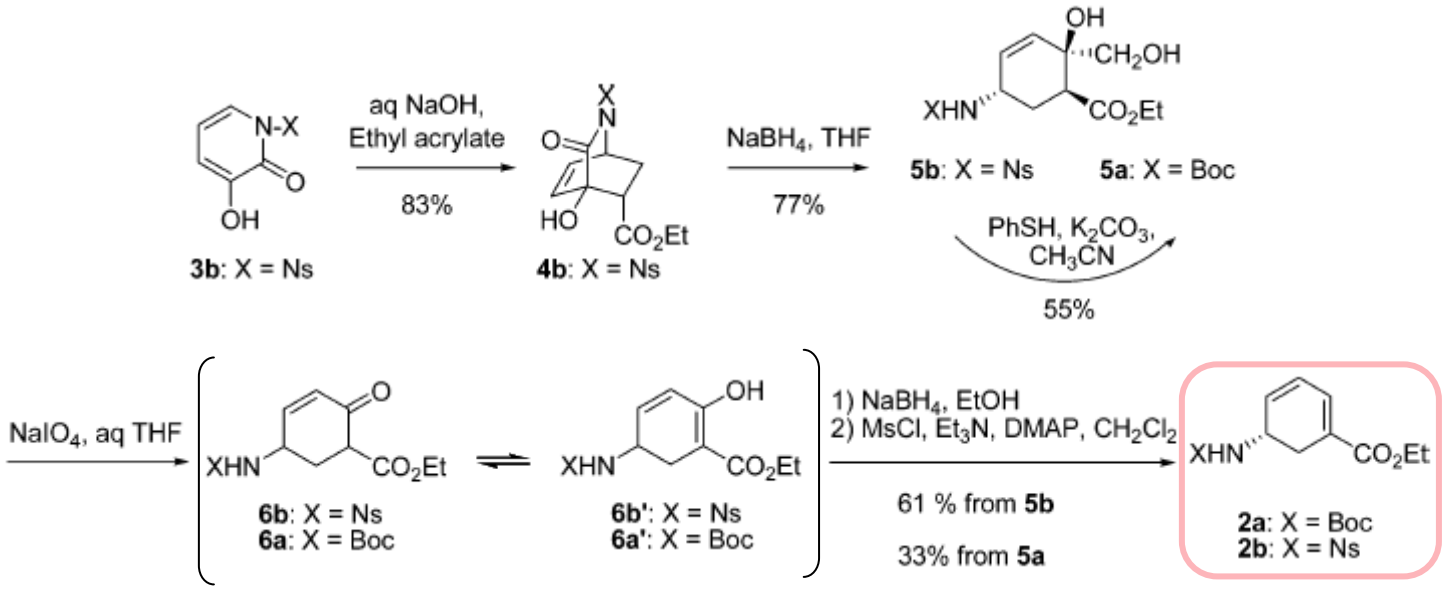
Yeung, Y.-Y.; Hong, S.; Corey, E. J.; *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.

Okamura study
for the synthesis of the Corey's intermediate



6: oseltamivir phosphate (R = Et)

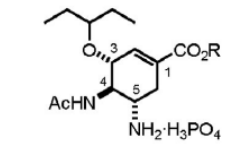
Corey's intermediate is synthetised by a base catalyzed Diels-Alder reaction



- starting material: 3-hydroxy-2-pyridones
- 6 steps for the intermediate, 11% for Boc, 39% for Ns
- key step: aqueous « green » Diels-Alder reaction
- chirality: studies are ongoing, asymmetric DA with acrylates having chiral auxiliaries have been reported by this group

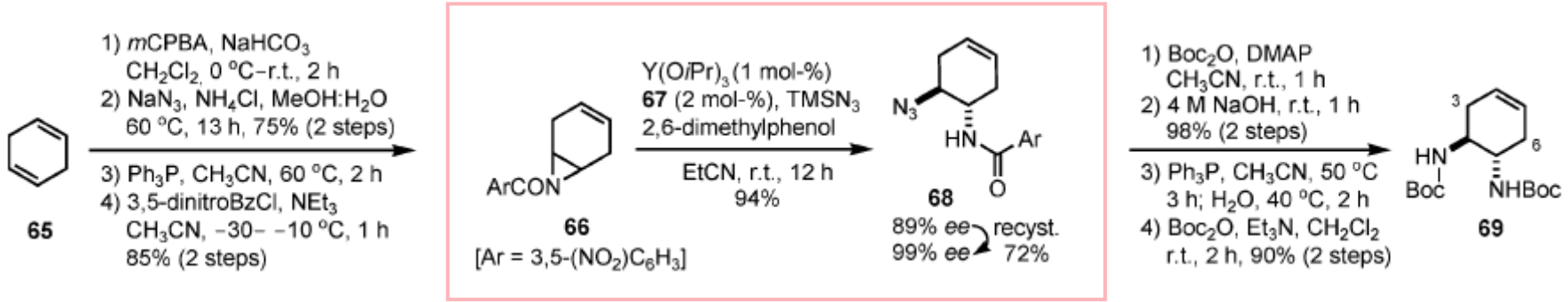
Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagana, T. *Org. Lett.* **2008**, *5*, 815-816.

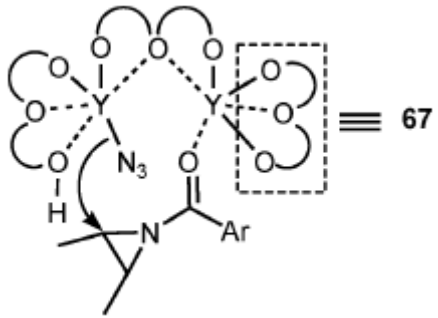
Shibasaki and Kanai synthesis
First generation (1/2)



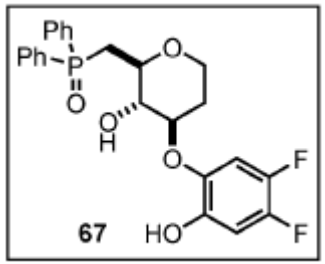
6: oseltamivir phosphate (R = Et)

Synthesis based on an asymmetric ring-opening of acyl-aziridine with azides



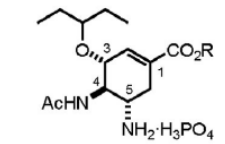


≡ **67**

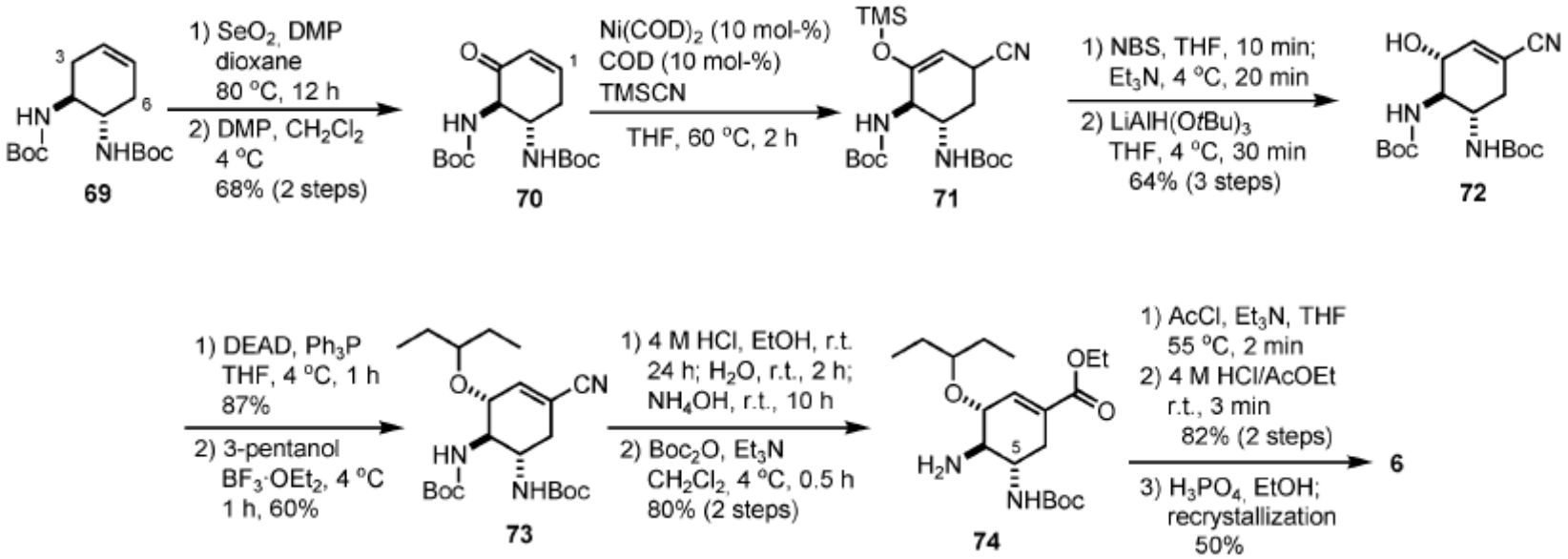


Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312–6313.

Shibasaki and Kanai synthesis
First generation (2/2)



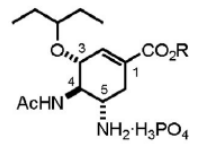
6: oseltamivir phosphate (R = Et)



- 17 steps, ~1%
- starting material: cyclohexadiene
- key steps: Ni catalyzed cyanation
- origin of the chirality: enantioselective opening of aziridine
- Drawback: over-manipulation of protecting groups

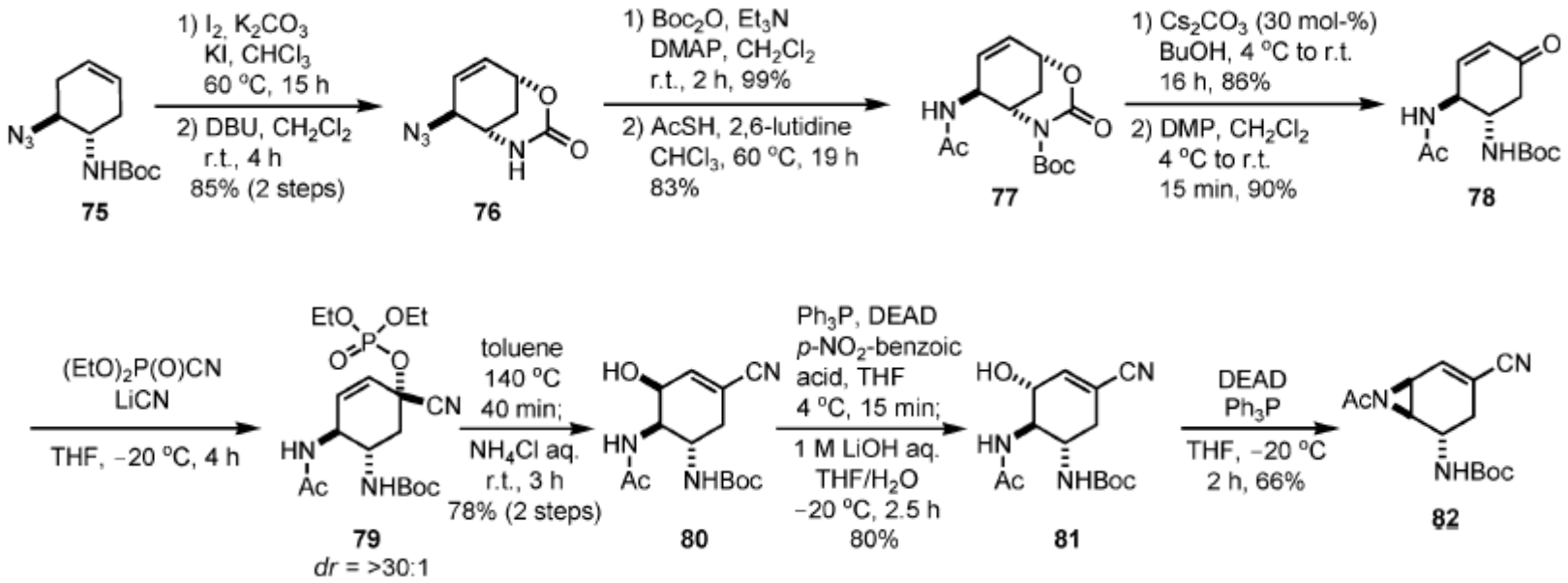
Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312–6313.

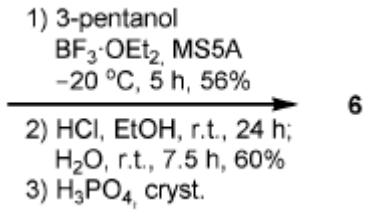
Shibasaki and Kanai synthesis
Second generation



6: oseltamivir phosphate (R = Et)

Synthesis starts with asymmetric ring-opening aziridine (see first generation synthesis)

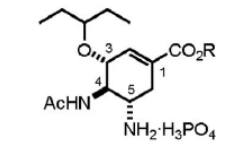




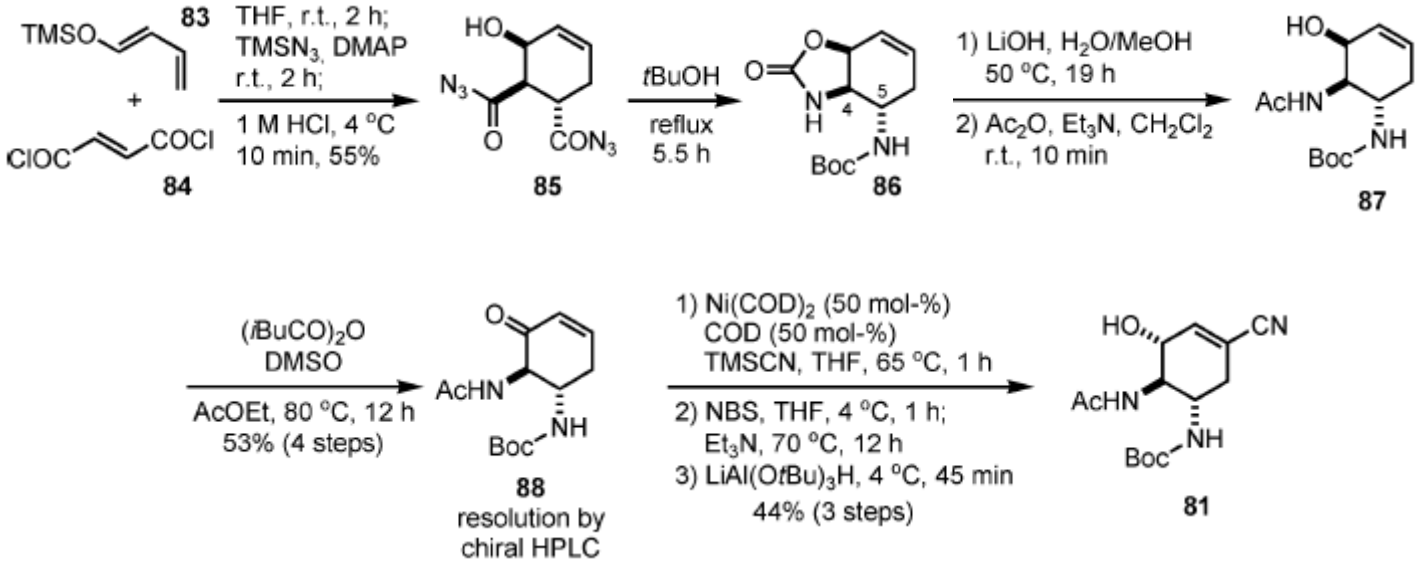
- 20 steps, ~7%
- starting material: cyclohexadiene
- key steps: cyanophosphorylation
- origin of the chirality: enantioselective opening of aziridine

Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259–262.

Shibasaki and Kanai synthesis
Third generation



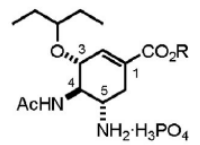
6: oseltamivir phosphate (R = Et)



- 12 steps, ~13%
- starting material: silyl ether diene and fumaroyl chloride
- key steps: Diels-Alder reaction, Curtius rearrangement
- origin of the chirality: resolution by chiral HPLC
- An enantioselective Diels-Alder reaction is currently ongoing

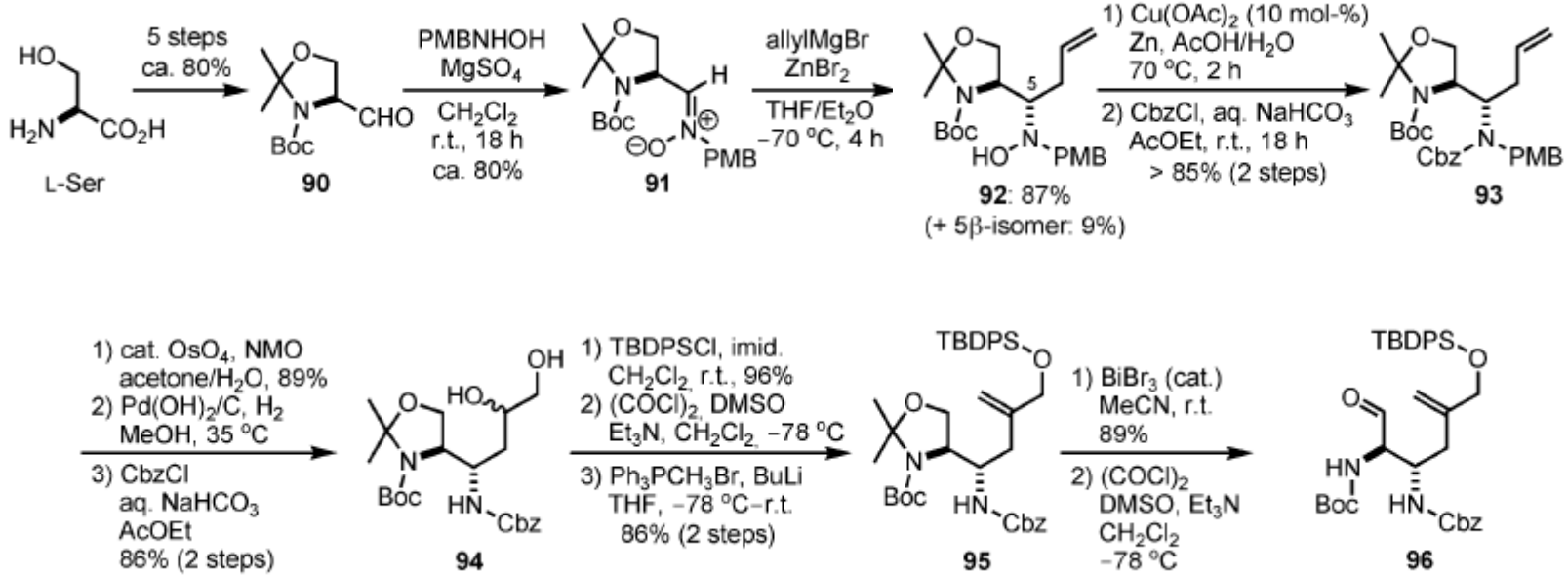
Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403–1406.

Yao synthetic study (1/2)



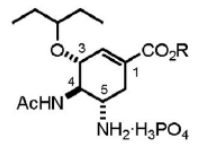
6: oseltamivir phosphate (R = Et)

Cyclic core of the target is built by RCM

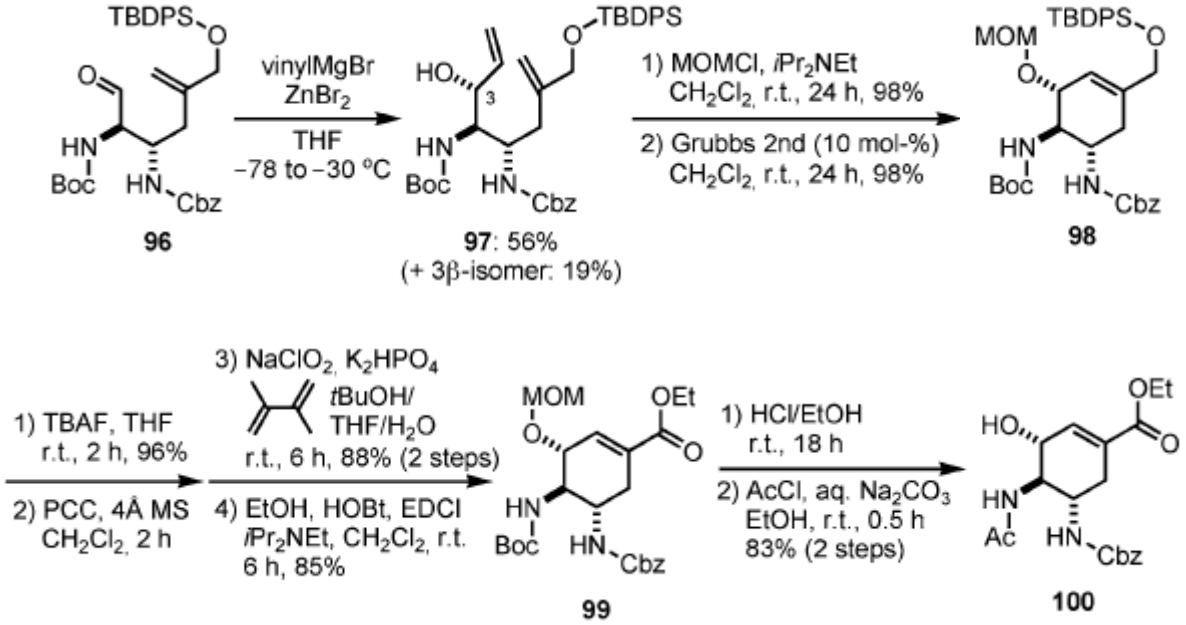


Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365–5368.

Yao synthetic study (2/2)



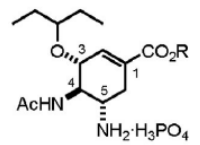
6: oseltamivir phosphate (R = Et)



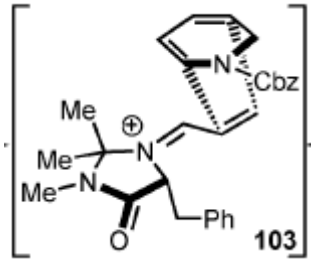
- starting material: L-serine / L-Gardner aldehyde
- key steps: Ring Closing Metathesis
- origin of the chirality: starting material
- Drawback: poor stereoselectivity

Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365–5368.

Fukuyama synthesis



6: oseltamivir phosphate (R = Et)



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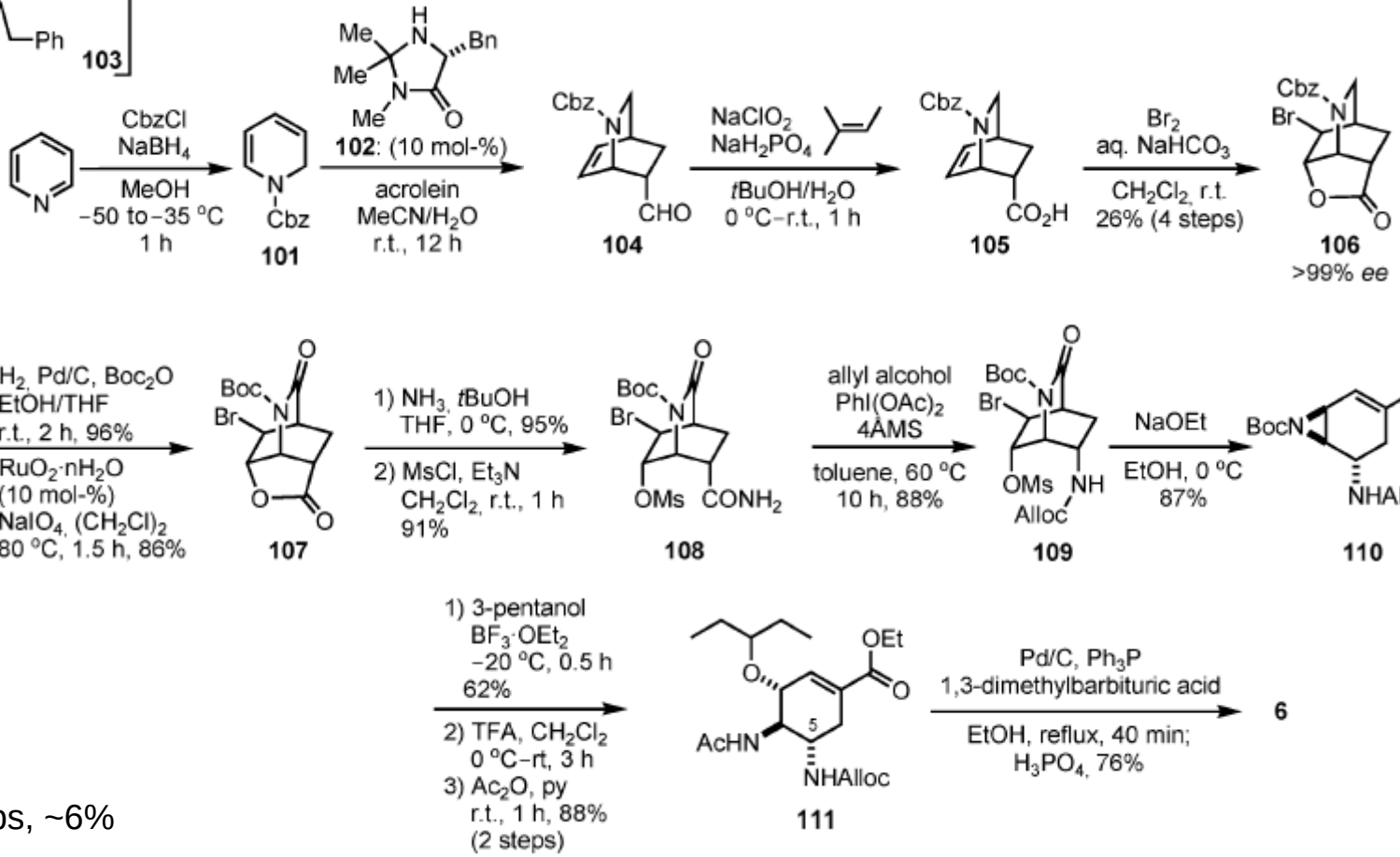
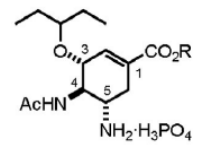


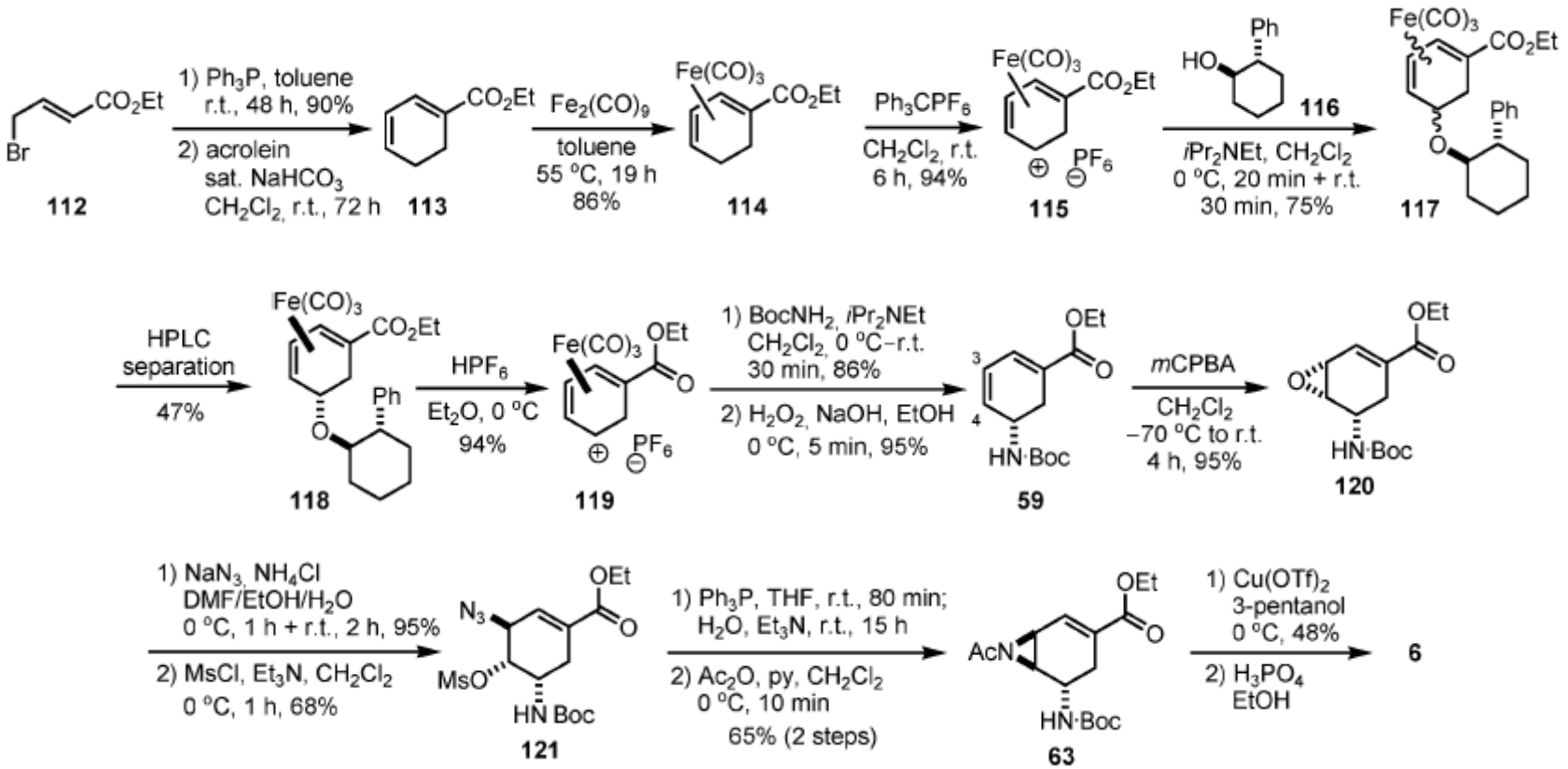
- 14 steps, ~6%
- starting material: pyridine
- key steps: Diels-Alder reaction
- origin of the chirality: asymmetric Diels-Alder reaction

Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734–5736, *Tetrahedron* **2008**, *in press*

Kann synthesis



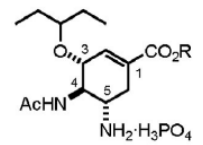
6: oseltamivir phosphate (R = Et)



- 16 steps, ~4%
- starting material: bromo-conjugated ester 112 and acroleine (cyclohexadiene)
- key steps: stereoselective amination of cationic iron carbonyl complex
- origin of the chirality: separation

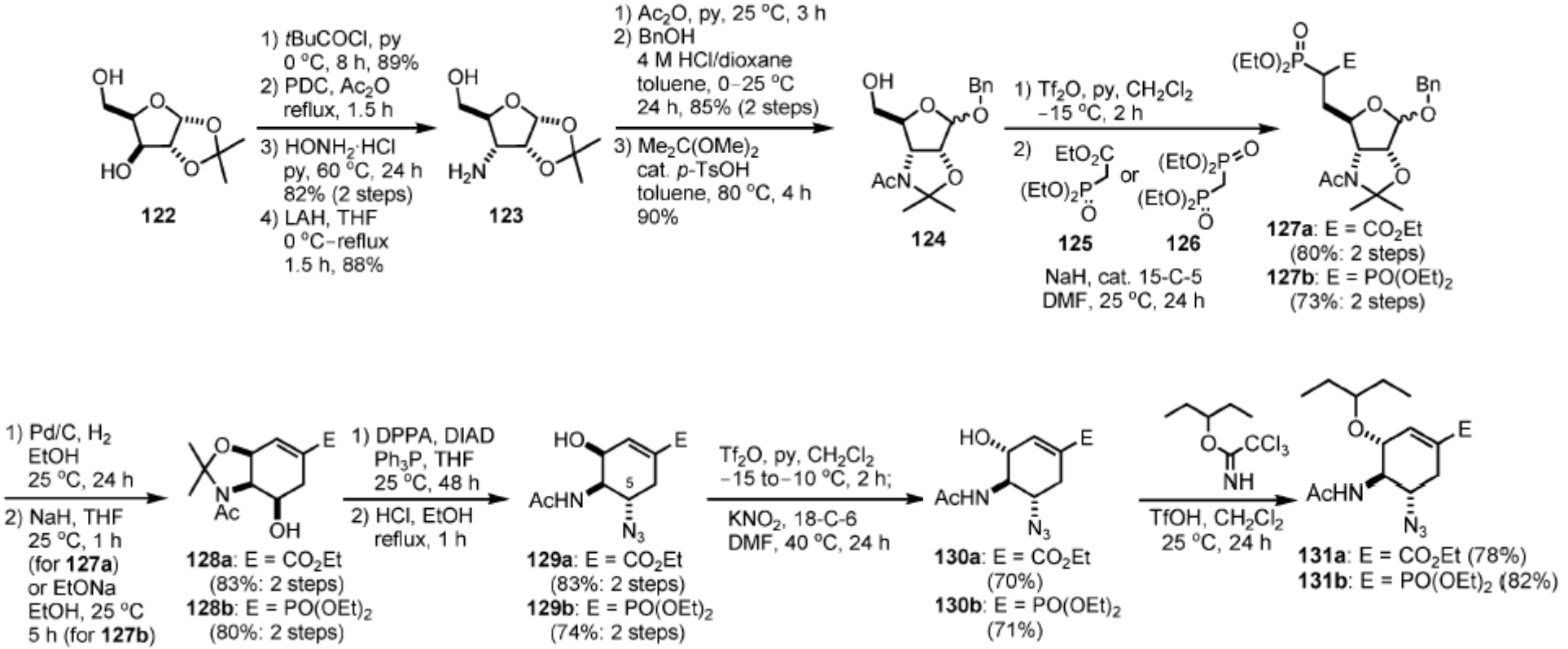
Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183–3185.

Fang synthesis (1/2)



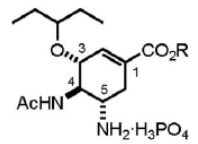
6: oseltamivir phosphate (R = Et)

Fang synthesis is done conjointly for Tamiflu and analogues

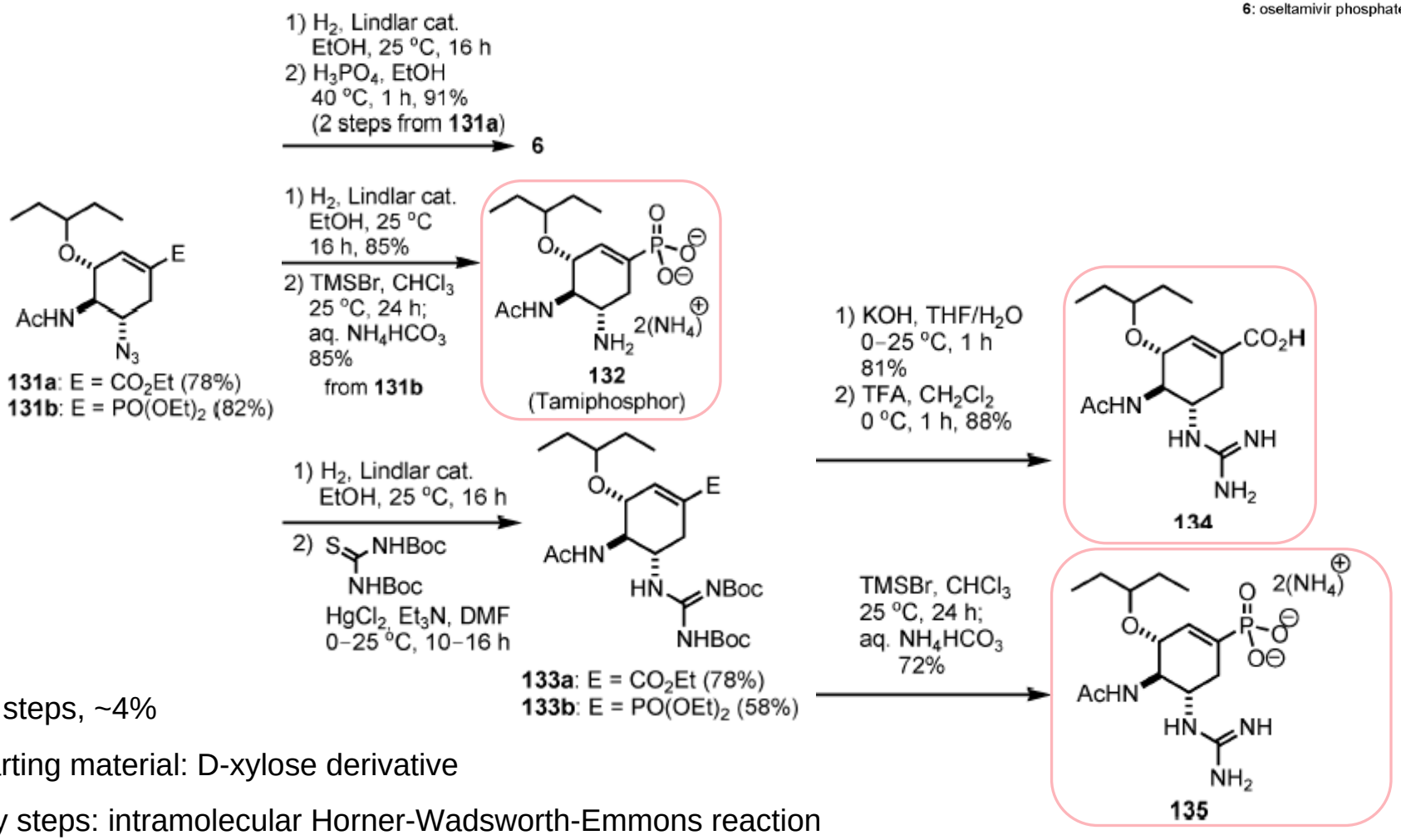


Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892–11893.

Fang synthesis (2/2)



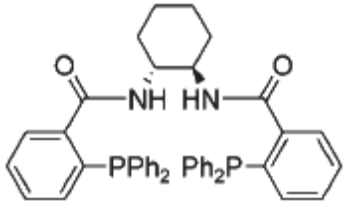
6: oseltamivir phosphate (R = Et)



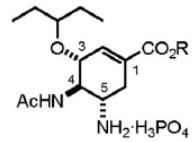
- 17 steps, ~4%
- starting material: D-xylose derivative
- key steps: intramolecular Horner-Wadsworth-Emmons reaction
- origin of the chirality: starting material
- Synthesis of phosphonate analogue and guanidine-containing compounds

Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892–11893.

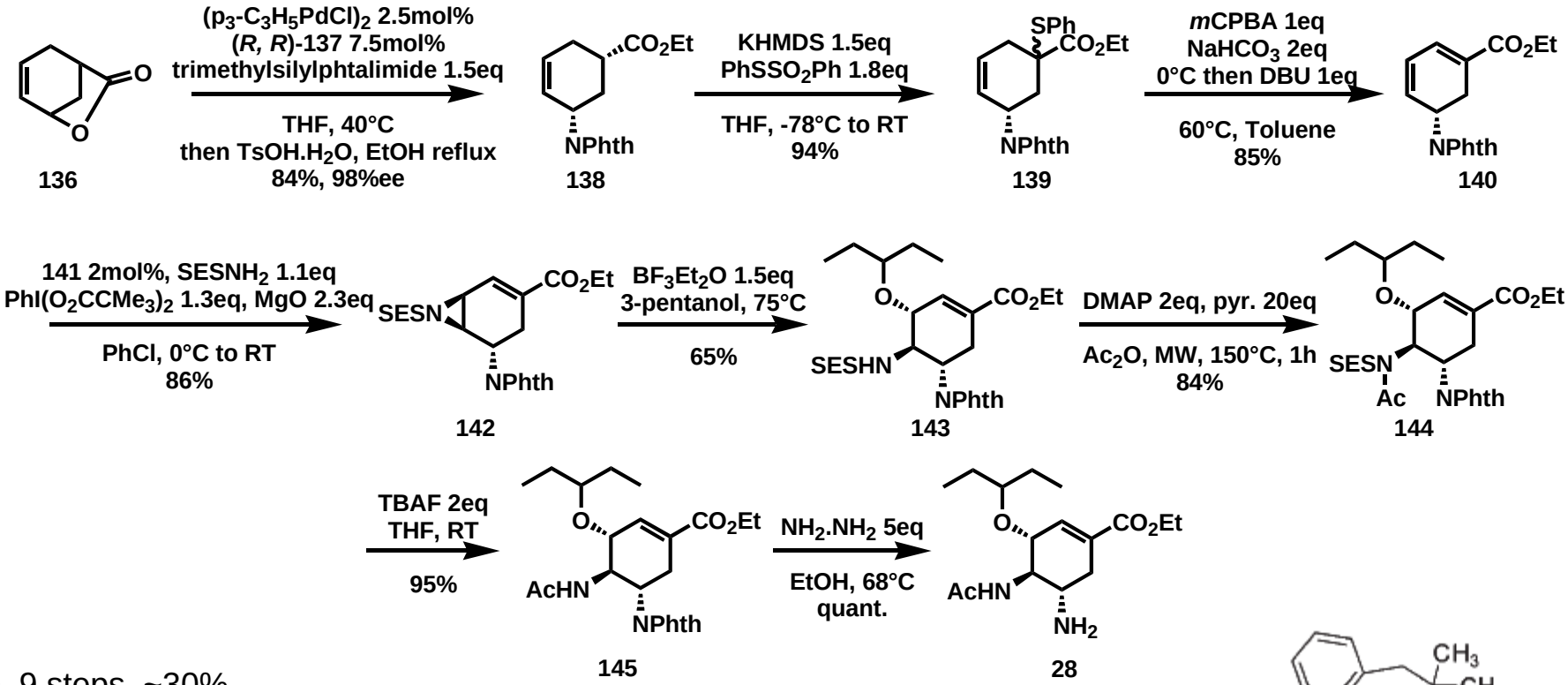
Trost synthesis



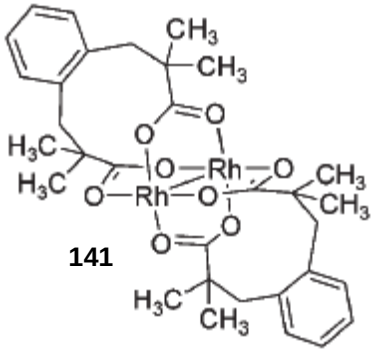
(*R, R*)-137



6: oseltamivir phosphate (R = Et)



- 9 steps, ~30%
- starting material: commercial lactone
- key steps: Pd-catalyzed allylic alkylation, Rh-catalyzed aziridination
- origin of the chirality: asymmetric allylic alkylation



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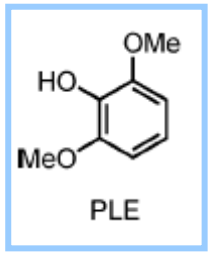
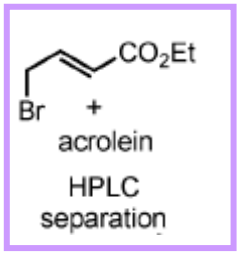
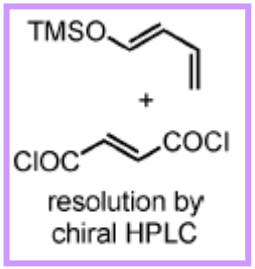
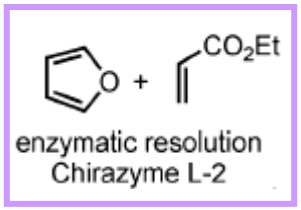
Trost B. M.; Zhang, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 3759 –3761

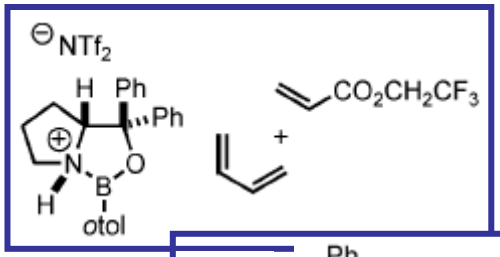
Synthesis of the Anti-influenza Drug Oseltamivir Phosphate (Tamiflu®)

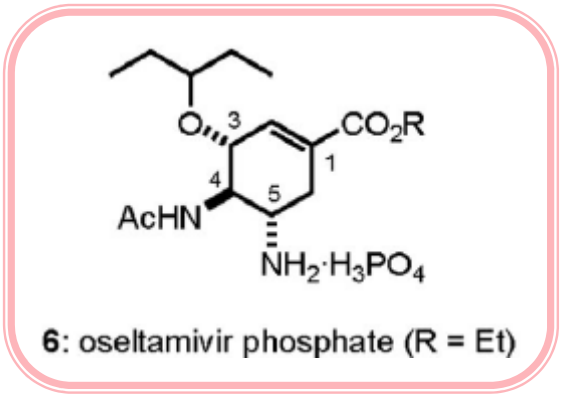


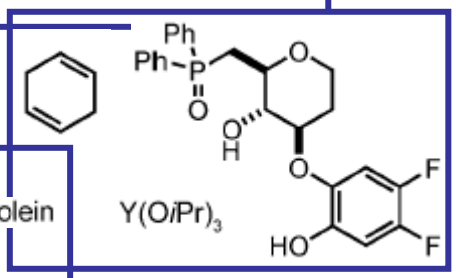


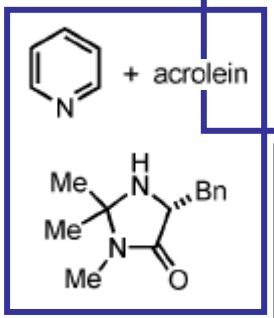


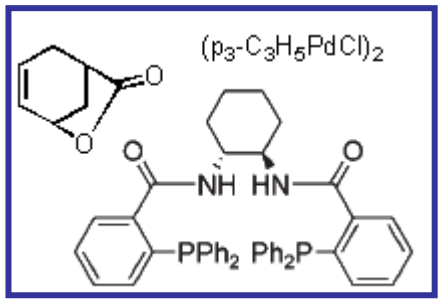


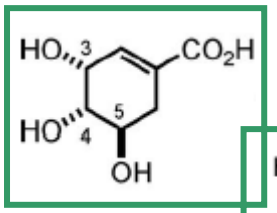


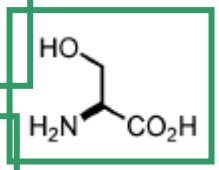


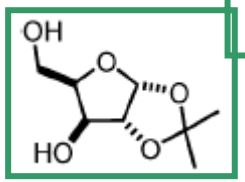












~10 years research

between 9 and 20 steps, around 30% overall yield