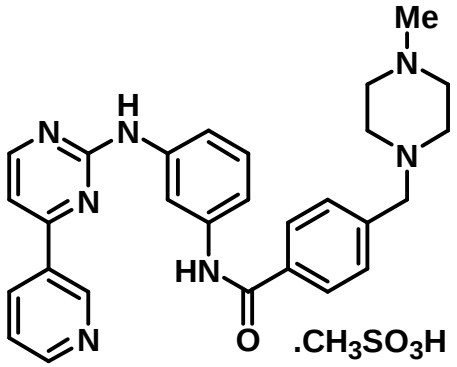
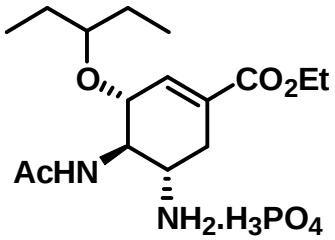
MASTER 2

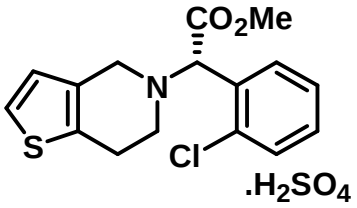
Molecular Chemistry – Medicinal Chemistry

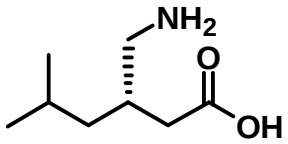
Université de Rennes 1 – Vietnam National University, Hanoi

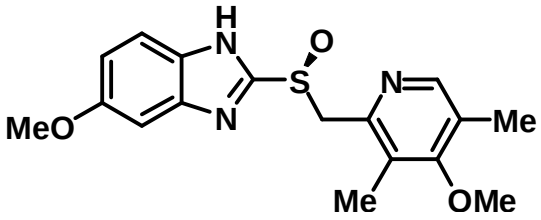
SYNTHESIS OF COMMERCIAL DRUGS











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2011-2012

INTRODUCTION

General Evolution of a Synthetic Route

Time

Discovery Phase "expedient" –

(Medicinal Chemistry): the identification and synthesis of a viable drug candidate

Development Phase "practical" –

- first kg for safety and early clinical studies. Typically uses the Med Chem route as a starting point

- pilot plant scale "efficient" production, 100's of kg

Marketing Phase "optimal" –

factory scale for commercialization, 1000's of kg

Chem. Rev. **2006**, *106*, 3002.

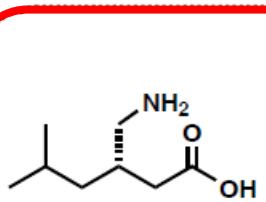
Rationale for changing a synthetic route can be assessed based on the SELECT criteria:

1) SAFETY
2) ENVIRONMENT
3) LEGAL
4) ECONOMICS
5) CONTROL
6) THROUGHPUT

SAFETY: "*if a route cannot be scaled up safely, then it should not be scaled up at all*"

Issues: thermal runaway
Gas evolution
Explosive or shock sensitive materials
Highly corrosive materials
Acute toxicity
Chronic toxicity
Genotoxicity
Pyrophoric/flammable materials

SYNTHESIS OF LYRICA (pregabalin)



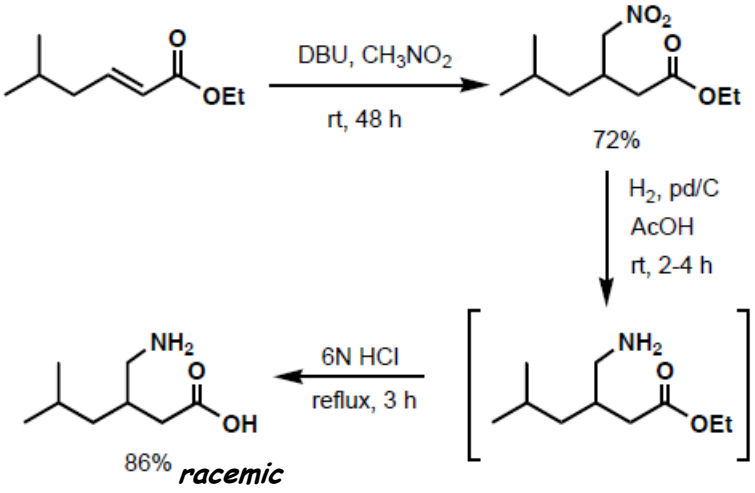
Lyrica
(pregabalin)

Pfizer (2004): nerve pain and epilepsy medication

Sales 2007 - $1.8 billion

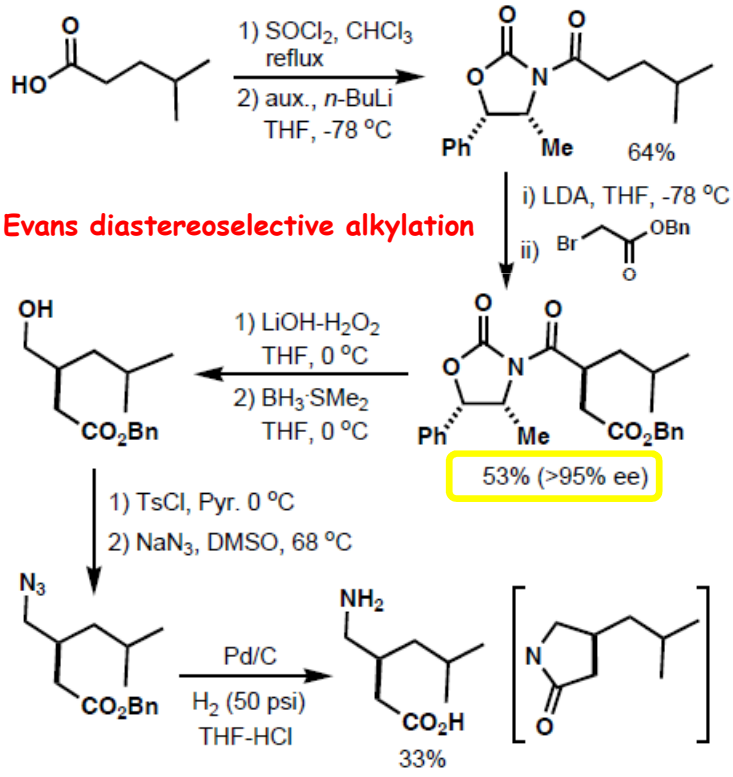
Off patent - 2018

***Original synthesis*: Silverman and Andruszkiewicz, 1989** *C&E News, 86(10), pg. 60*

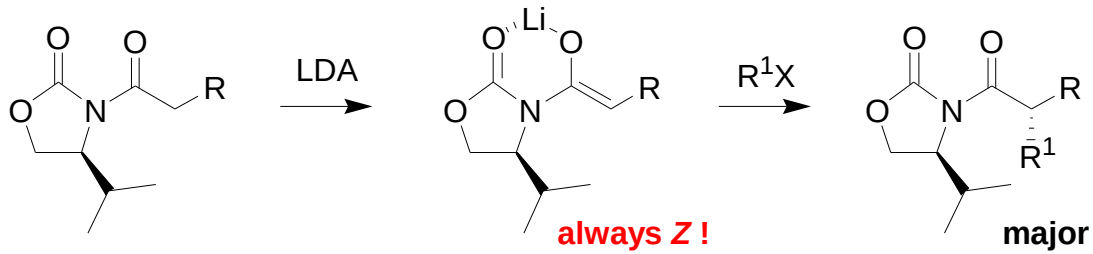


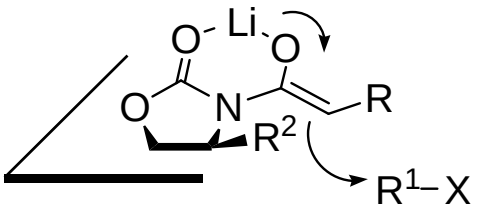
Pregabalin was soon licensed to Parke-Davis (later acquired by Pfizer)

Discovery Route: *Bioorg. Med. Chem. Lett.* **1994**, *6*, 823



Evans diastereoselective alkylation = a very powerfull tool for asymmetric synthesis

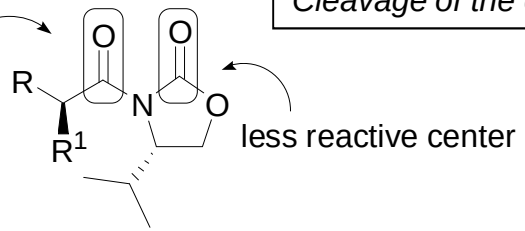




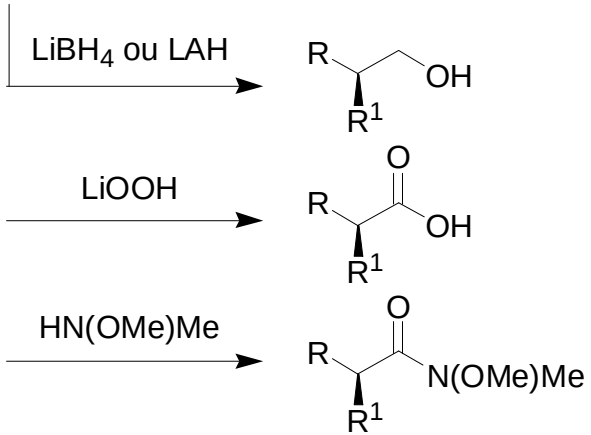
The addition of the enolate to the electrophile occurs on the less sterically hindered face, that is to say, on the opposite side to the R^2 group of the chiral auxiliary.

Cleavage of the chiral auxiliary

carbonyl more reactive than a classical amide



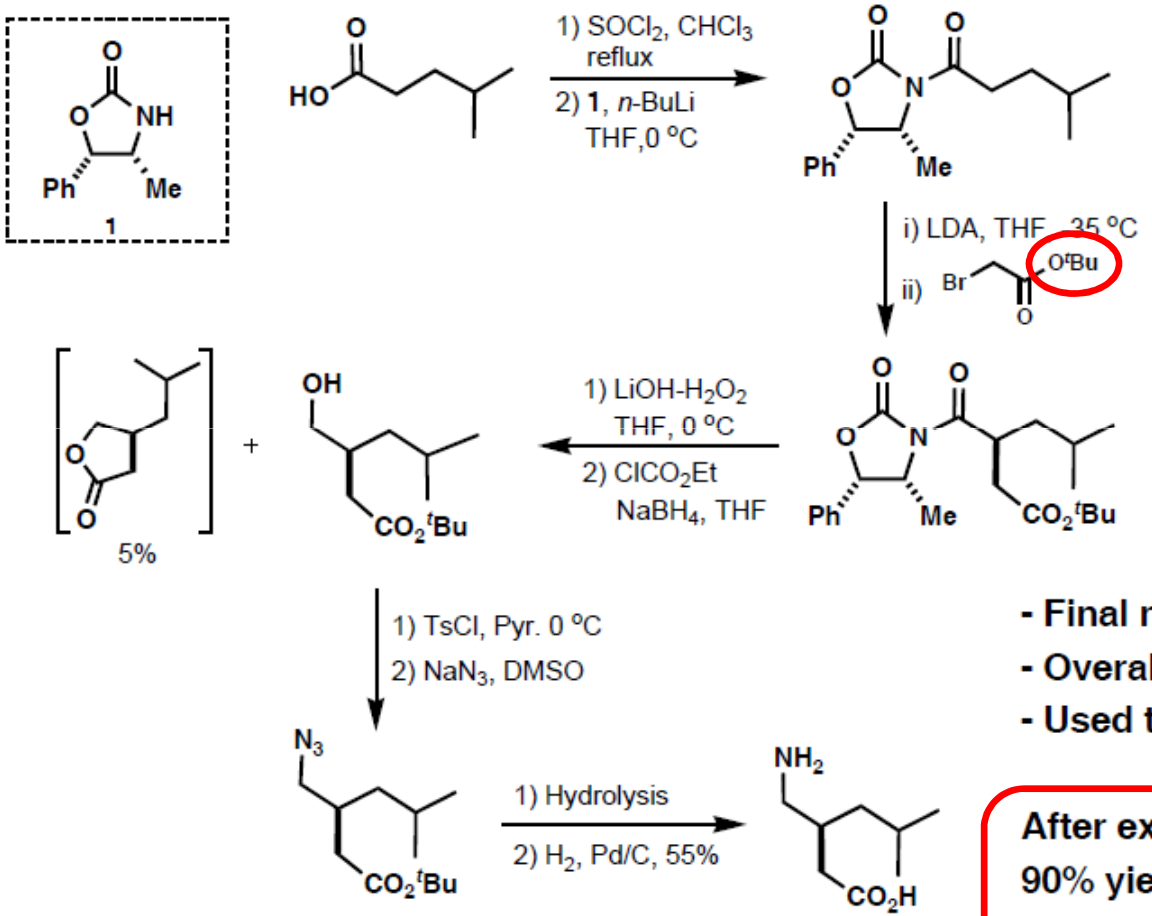
less reactive center



Evans, D.A. et coll. *J. Am. Chem. Soc*. **1982**, *104*, 1737 and lecture of René Grée

SYNTHESIS OF LYRICA (pregabalin)

Modified Discovery Route:

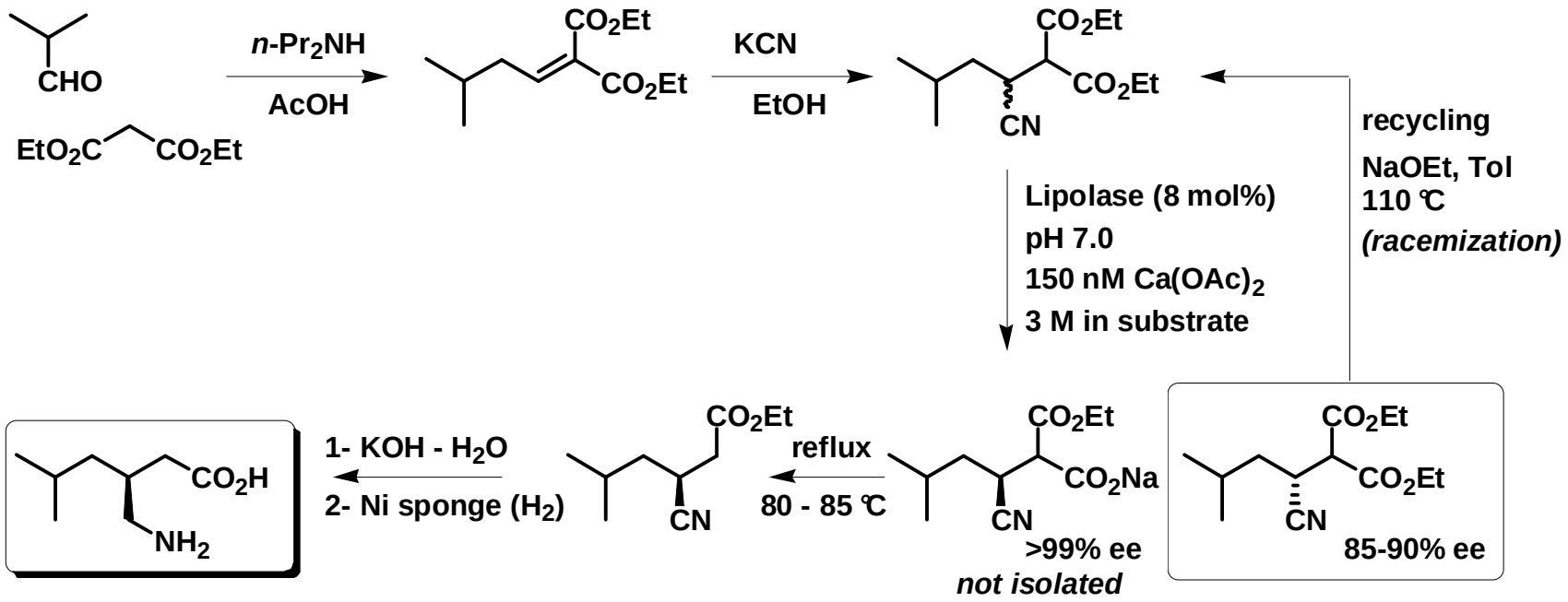


- Final neutral hydrogenation
- Overall yield improved to 33%
- Used to prepare 100's kg

After extensive optimization: average 90% yield per step, but still 10 linear steps and 6x the desired cost factor…not good enough!

SYNTHESIS OF LYRICA (pregabalin)

Manufacture route

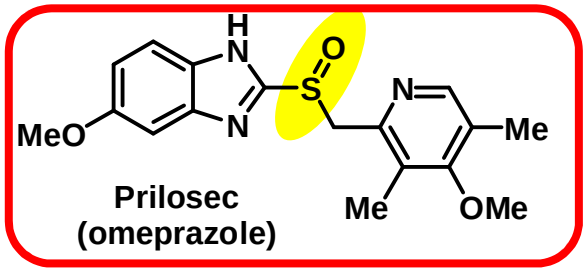


99.5% purity
99.75% ee

40-45% overall yield after one recycle
*All reaction run in aqueous media
*Ratio of kg waste/kg pregabalin produced
Classical resolution route 86:1
Chemoenzymaticroute 17:1
*Solvent use per 1000 kg pregabalin
Classical resolution route 50,042 kg
Chemoenzymatic route 6230 kg

Org. Proc. Res. Dev. **2008**, *12*, 392.

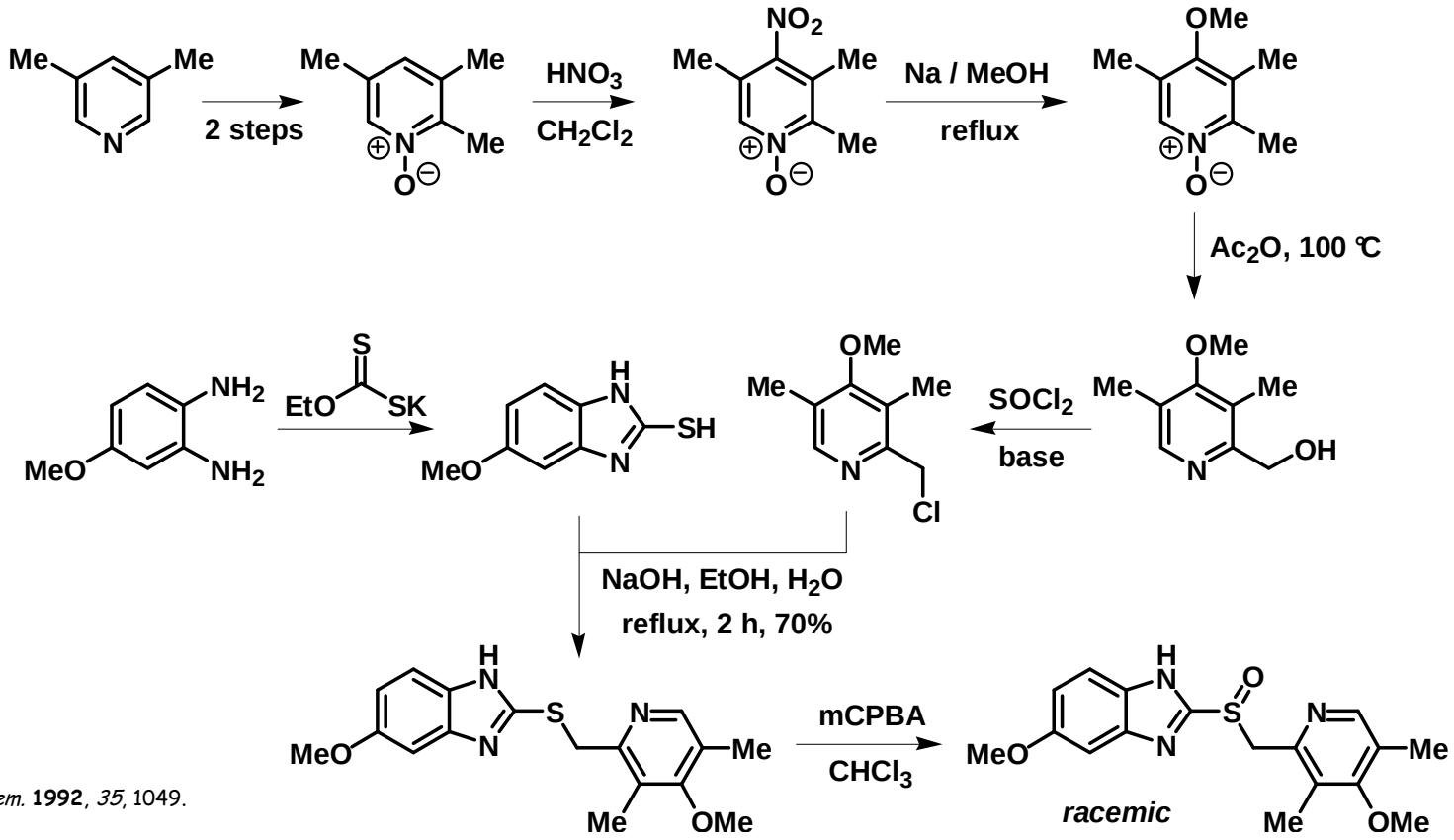
SYNTHESIS OF PRILOSEC-NEXIUM (omeprazole-esomeprazole)



Prilosec (omeprazole)

Astra Zeneca (1985)
Proton pomp inhibitor used in the treatment of gastric reflux disease
Sales 2007 = $5 billion
Off patent in 2014

First synthesis : preparation in racemic form



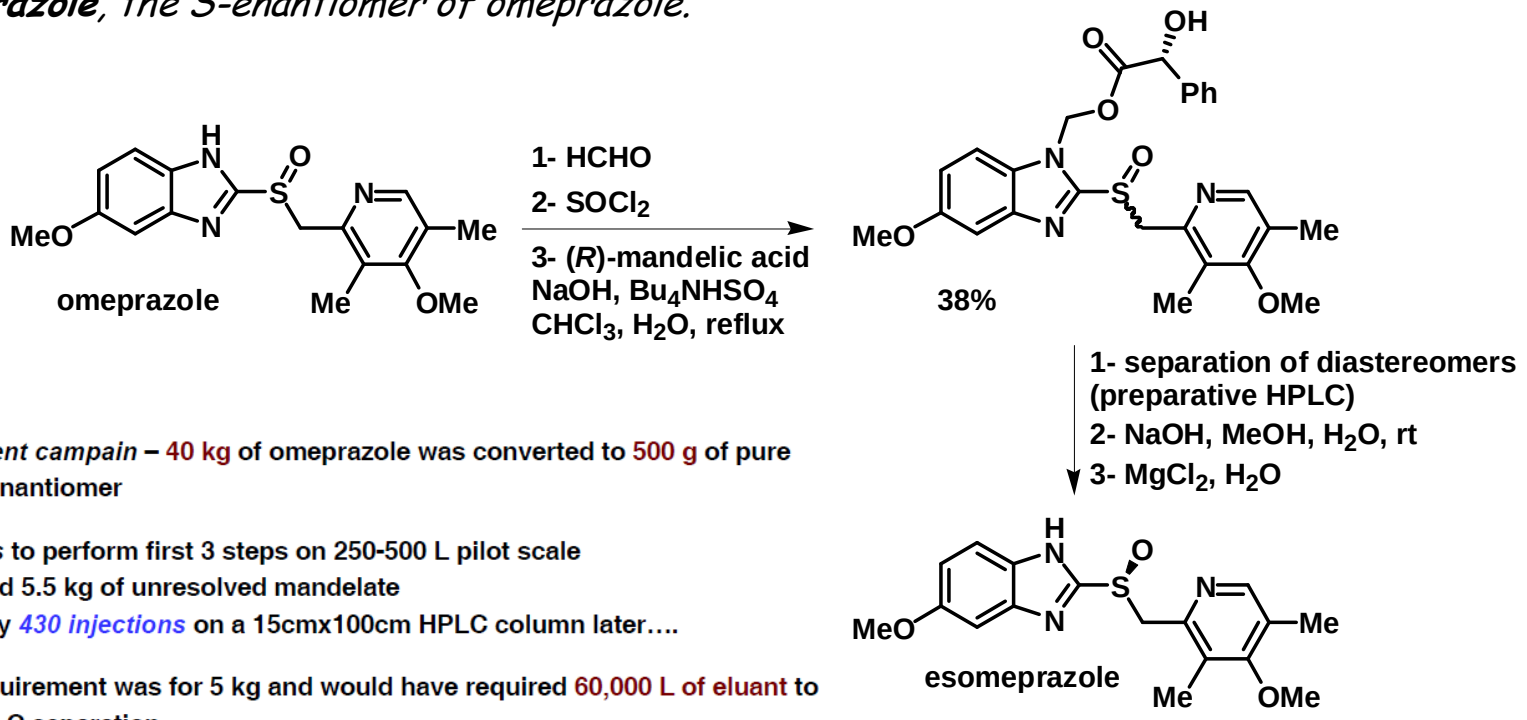
J. Med. Chem. **1992**, *35*, 1049.

SYNTHESIS OF PRILOSEC-NEXIUM (omeprazole-esomeprazole)

Improvement : omeprazole to esomeprazole

1987 – Prilosec found to display significantly varying efficacy depending on rate of metabolism of patient.
Program launch to find a compound with increased bioavailability that won't be cleared by the liver so quickly to give "slow metabolizers"a chance
1989-1994 – 30 scientists and several hundred compounds later…four candidates are identified

Only *one compound survives pharmacokinetics, efficacy and safety assessments…* ***esomeprazole****, the S-enantiomer of omeprazole.*



First development campain – 40 kg of omeprazole was converted to 500 g of pure esomeprazole enantiomer

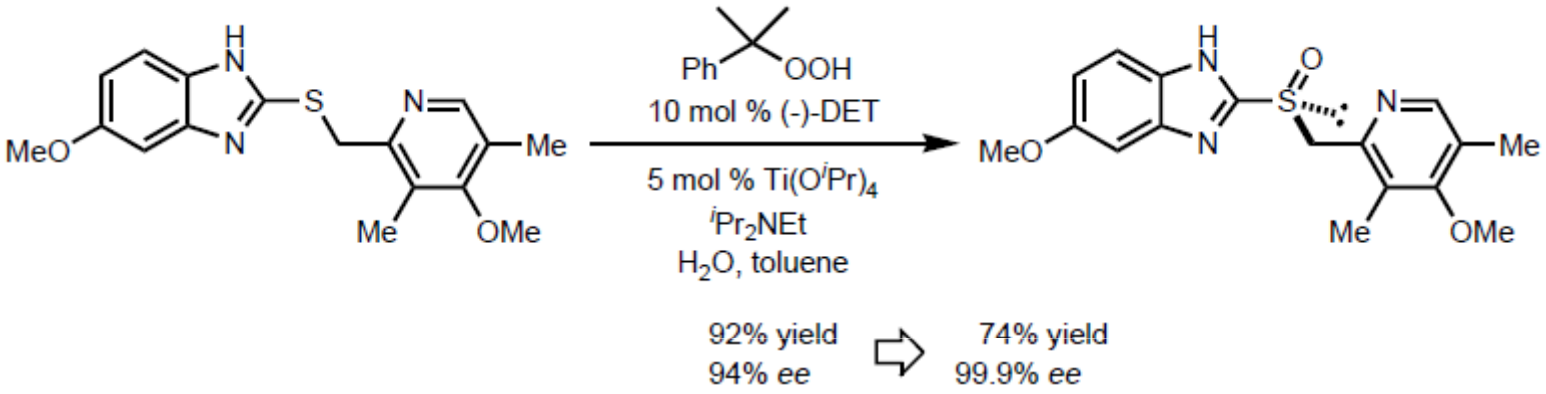
- *6 weeks* to perform first 3 steps on 250-500 L pilot scale
- provided 5.5 kg of unresolved mandelate
- and only *430 injections* on a 15cmx100cm HPLC column later….

Next supply requirement was for 5 kg and would have required 60,000 L of eluant to support the HPLC separation

SYNTHESIS OF PRILOSEC-NEXIUM (omeprazole-esomeprazole)

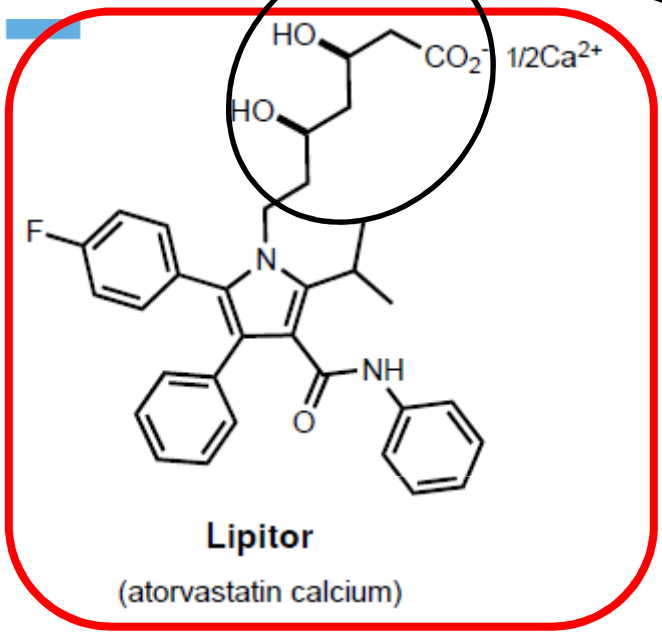
Improvement : omeprazole to esomeprazole

Formation of the sulfoxide by using of the Kagan's oxidation (Sharpless oxidation modified)



route	steps from sulfur	manufacture of esomeprazole (5 kg in plant)
medicinal route	6	14 weeks
new route	1	2 weeks

SYNTHESIS OF LIPITOR (atorvastatin calcium)



Lipitor

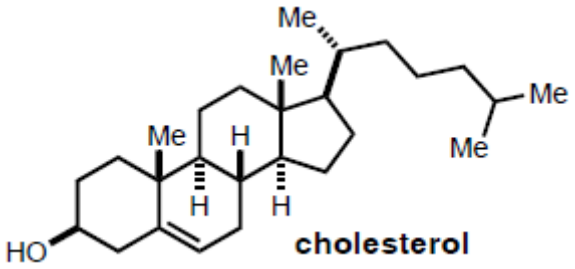
(atorvastatin calcium)

Pfizer (1997): treatment of hypercholesterolemia via inhibition of cholesterol biosynthesis

Sales 2007 - $ 12.7 billion

Off Patent - 2011

Chiral side chain : 220 ton / year



cholesterol

Cholesterol: a very important biological molecule
-most cholesterol is not dietary, it is synthesized internally.
-cholesterol is bound to lipoproteins and transported through blood.
-2 kinds of lipoproteins:
-high density lipoprotein (HDL): "good"
- low density lipoprotein (LDL): "bad"

↓

atherosclerosis

↓

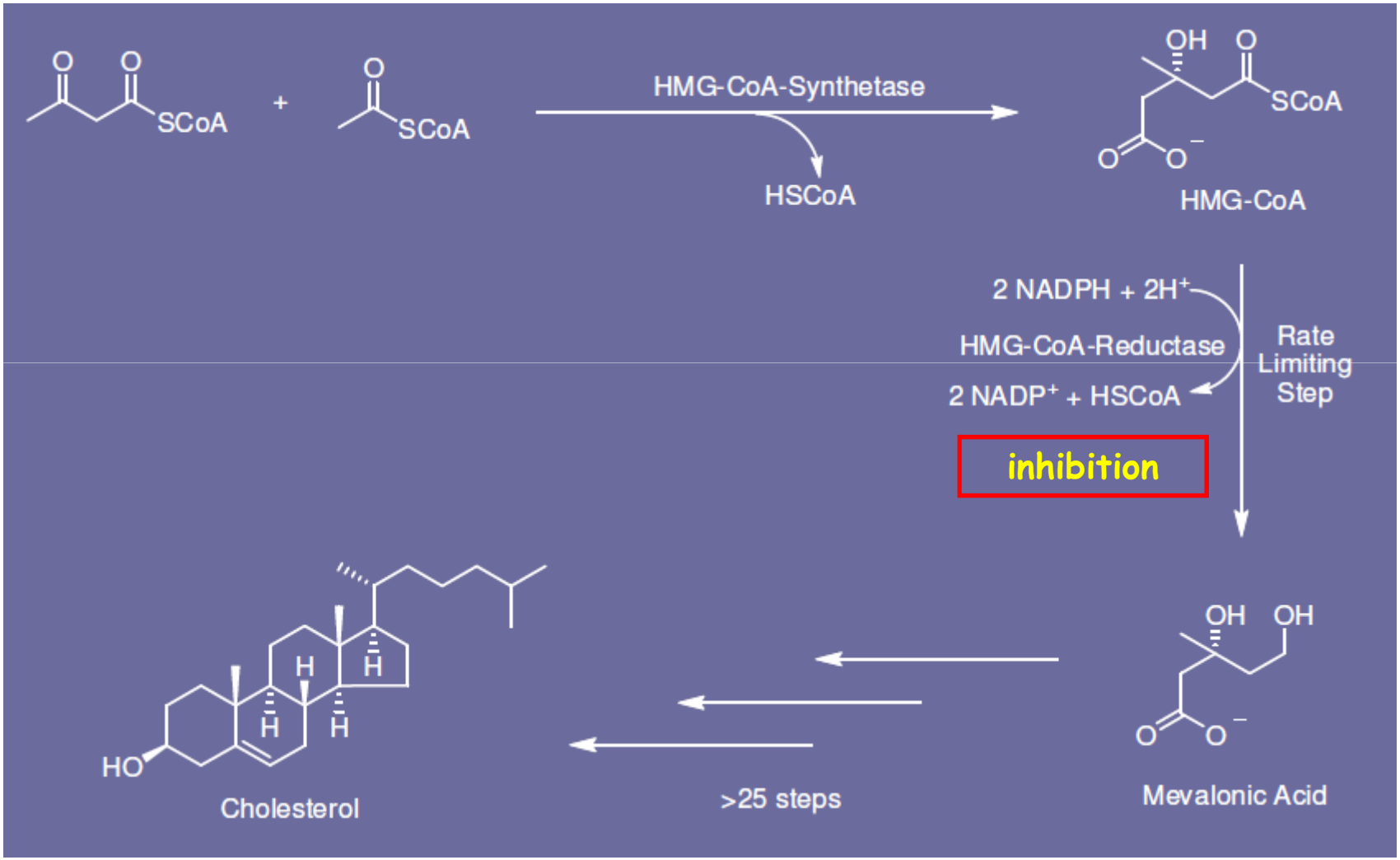
coronary heart disease & other cardiovascular diseases

↓

One of the leading causes of death in the world today!

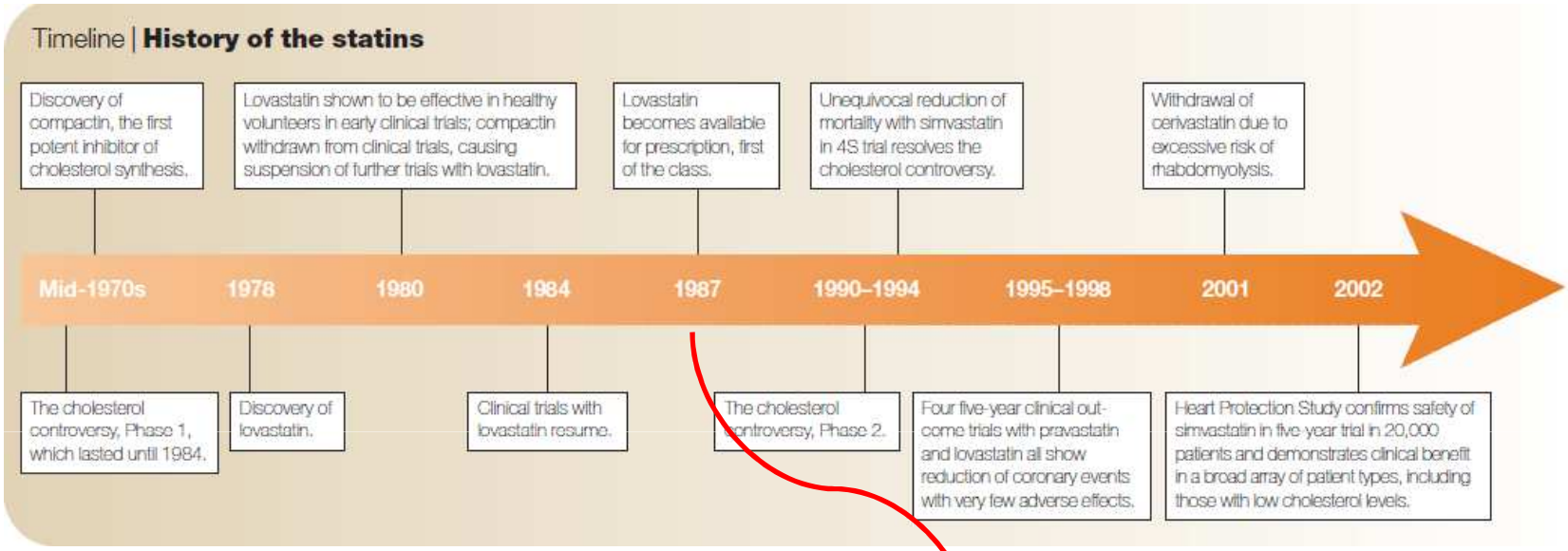
SYNTHESIS OF LIPITOR (atorvastatin calcium)

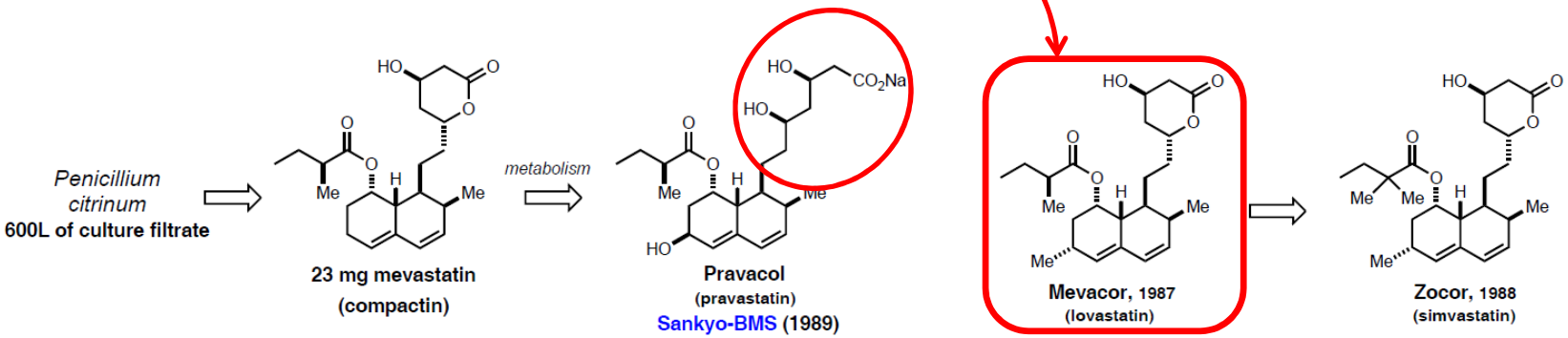
A solution: the suppression of the cholesterol biosynthesis



SYNTHESIS OF LIPITOR (atorvastatin calcium)

The story of statins drugs

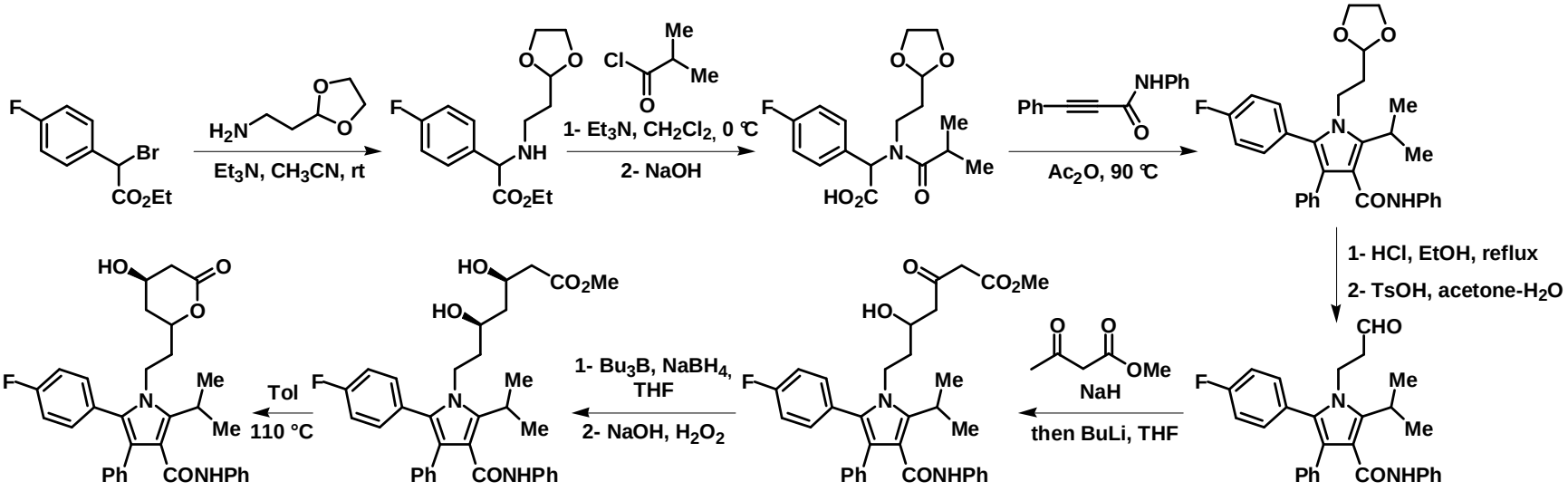




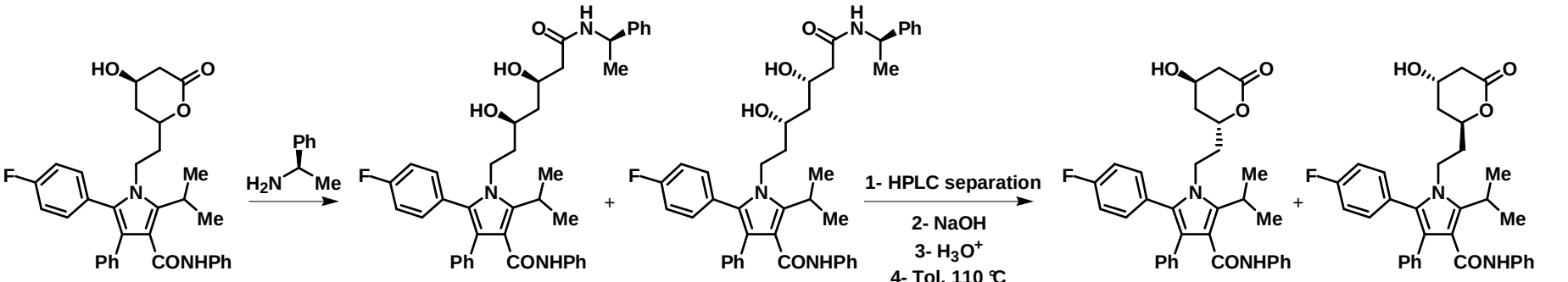
Potent inhibitors of HMG-CoA reductase

SYNTHESIS OF LIPITOR (atorvastatin calcium)

The synthesis of atorvastatin lactone

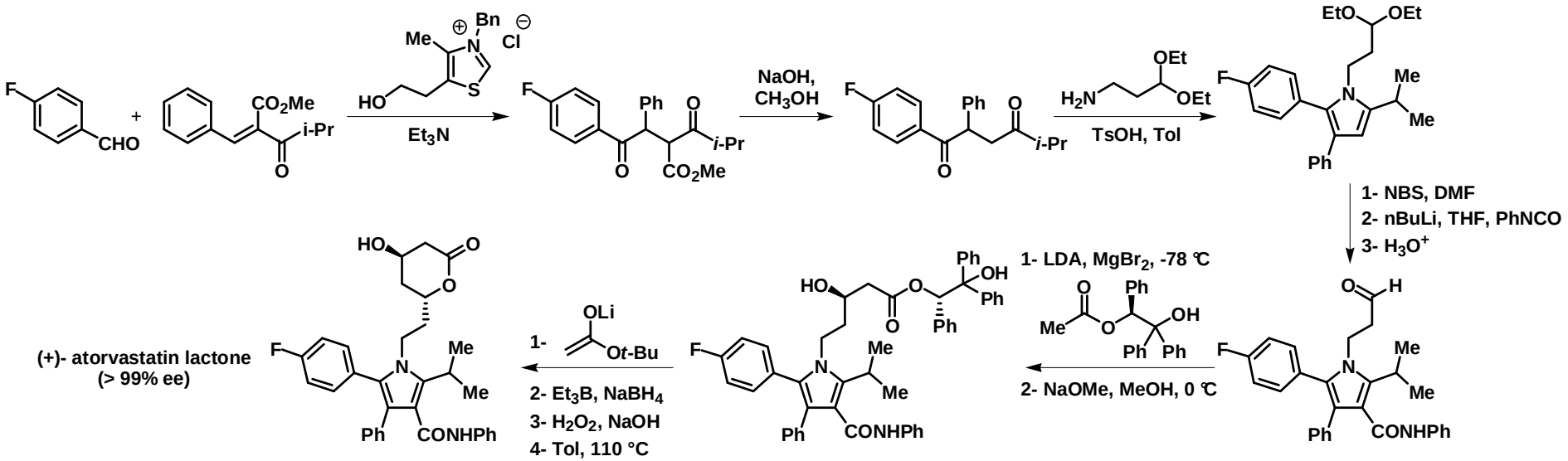


Separation of enantiomers
(resolution via diastereomeric esters synthesis)



SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin lactone (labor approach)



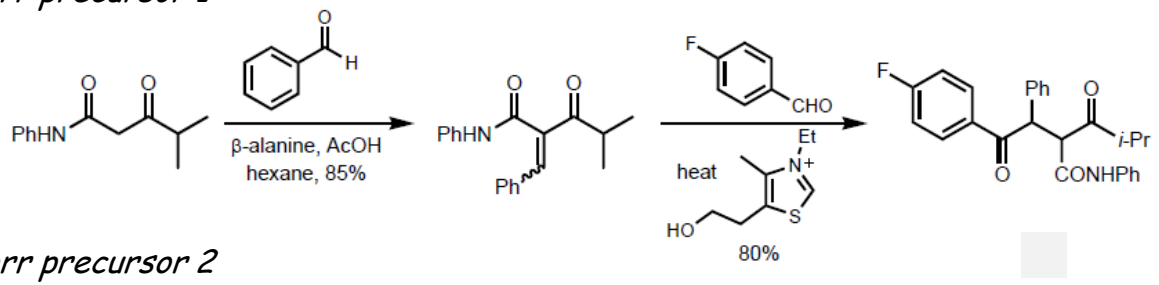
12 linear steps
3 columns and 1 recrystallization
Low temperature steps
Low yields
Low yielding final purification

Poor potential for kg scale

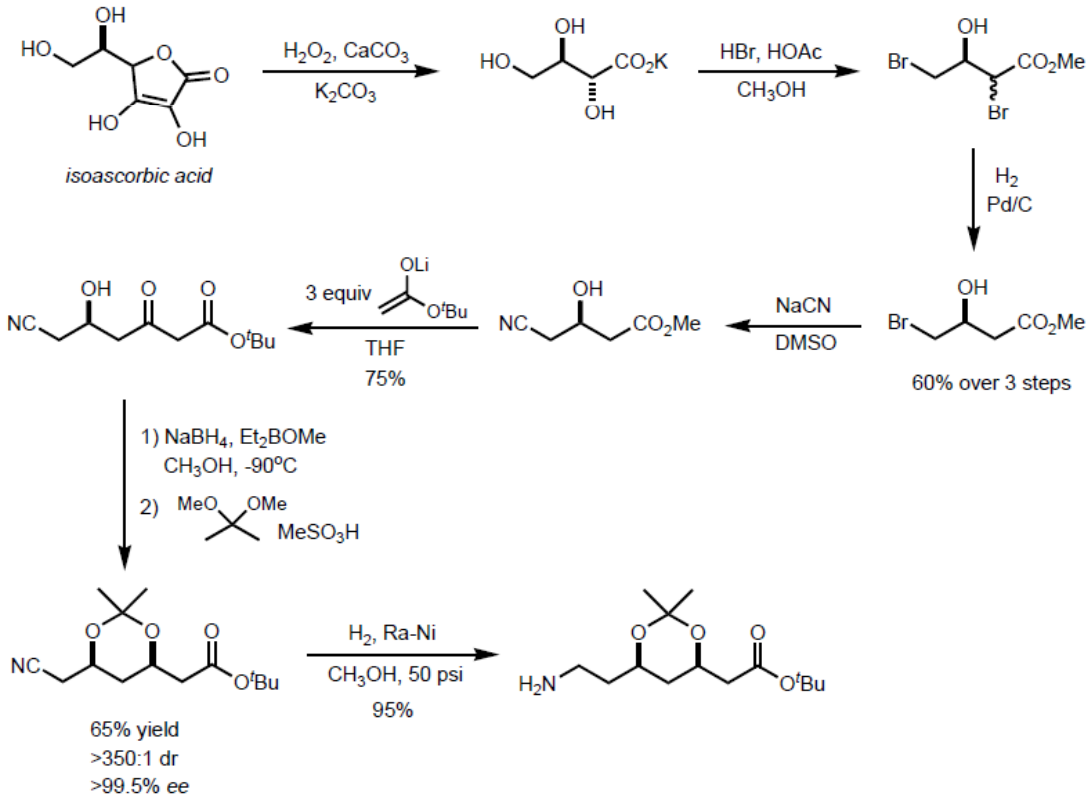
SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin calcium: the solution

Synthesis of Paal-Knorr precursor 1



Synthesis of Paal-Knorr precursor 2



SYNTHESIS OF LIPITOR (atorvastatin calcium)

The enantioselective synthesis of atorvastatin calcium : the solution (2)

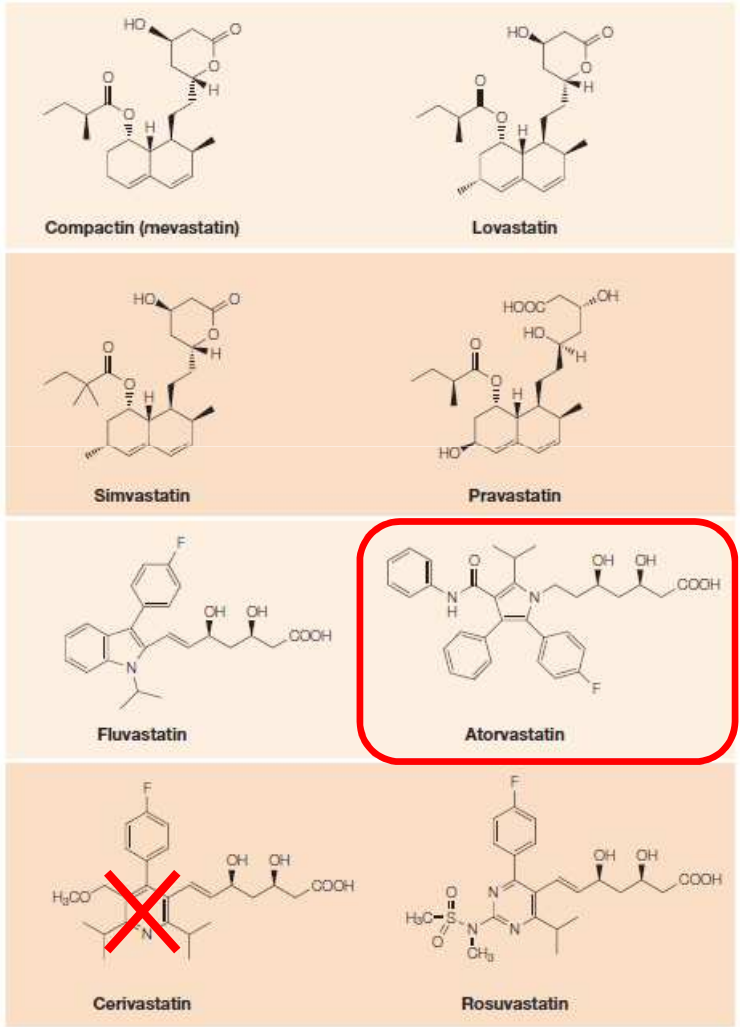
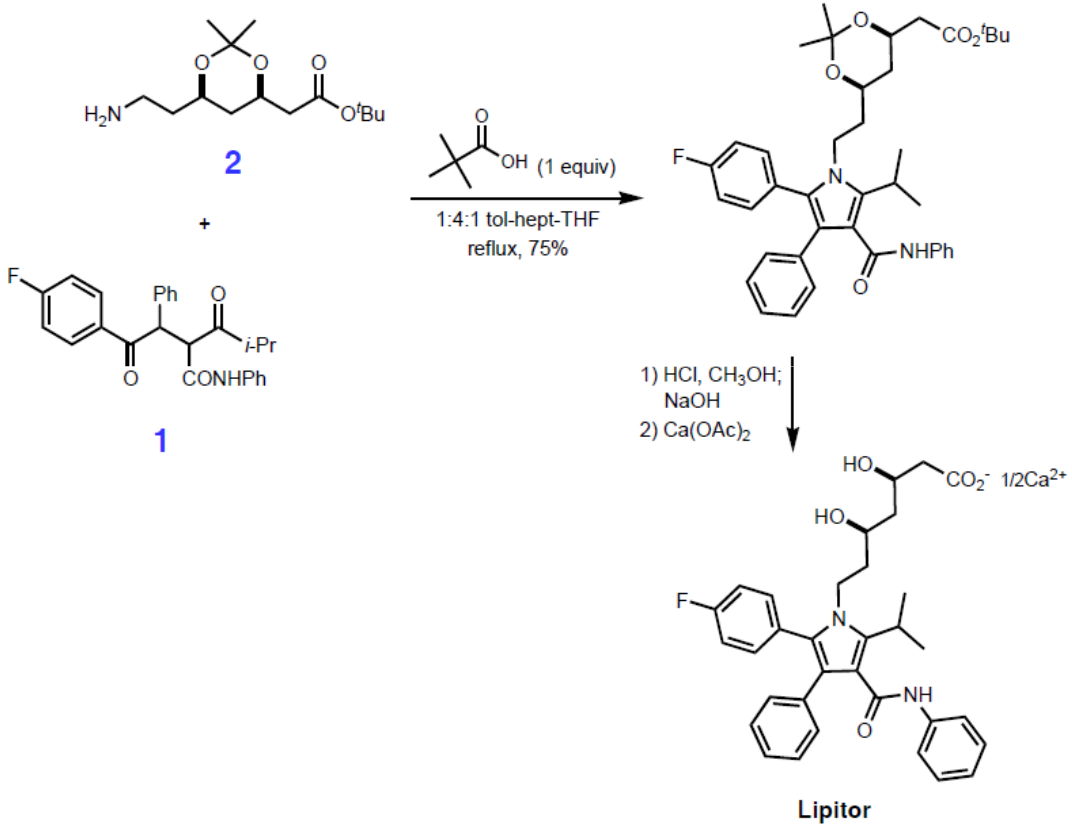
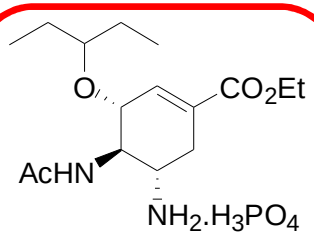


Figure 3 | **Structures of the statins.** Compactin and lovastatin are natural products. Pravastatin is derived from compactin by biotransformation, and simvastatin is a semisynthetic derivative of lovastatin. All other statins shown are totally synthetic.



SYNTHESIS OF TAMIFLU (oseltamivir phosphate)



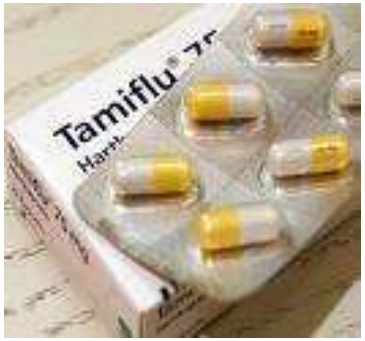
Osetalmivir Phosphate
Tamiflu

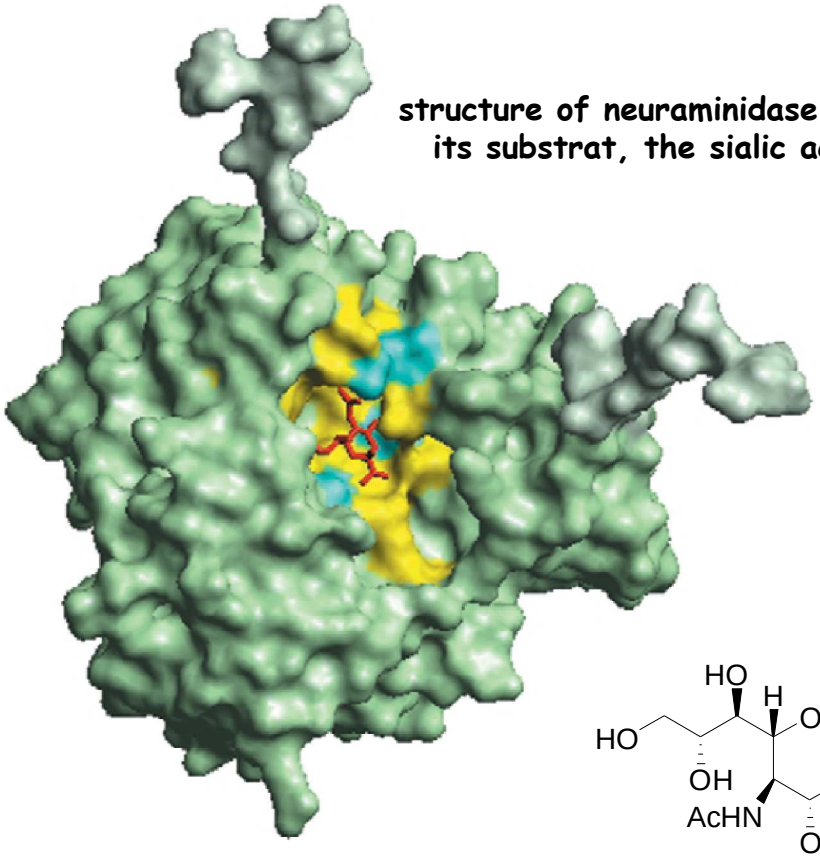
Roche (1995)

Anti-viral drug to slow the spread of the Influenza virus

Sales 2009 = 2.7 billion €

Review = *Chem. Rev.* **2009**, *109*, 4398





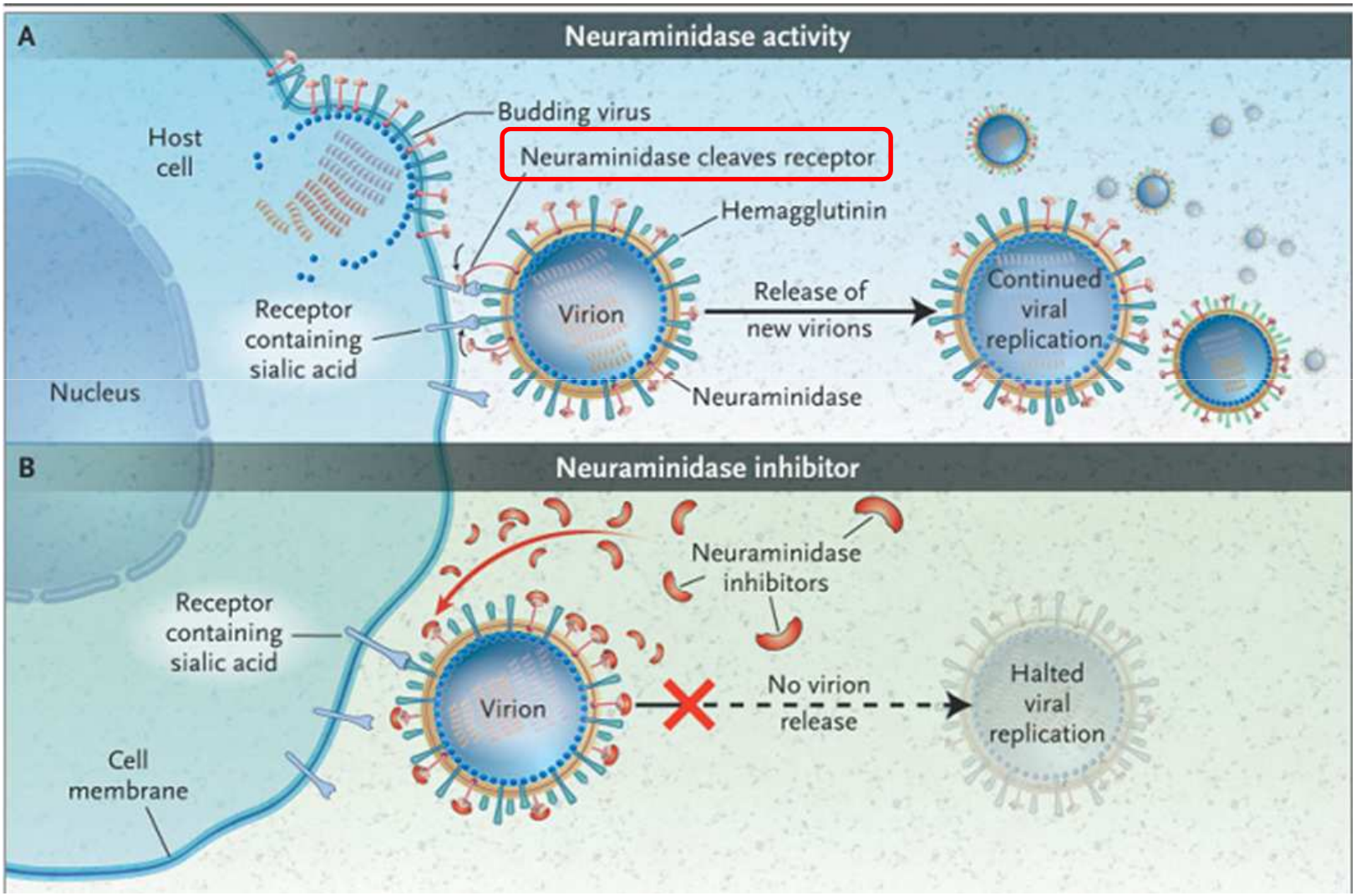
structure of neuraminidase with its substrat, the sialic acid

sialic acid
(*N*-acetylneuraminic acid)

towards the drug design

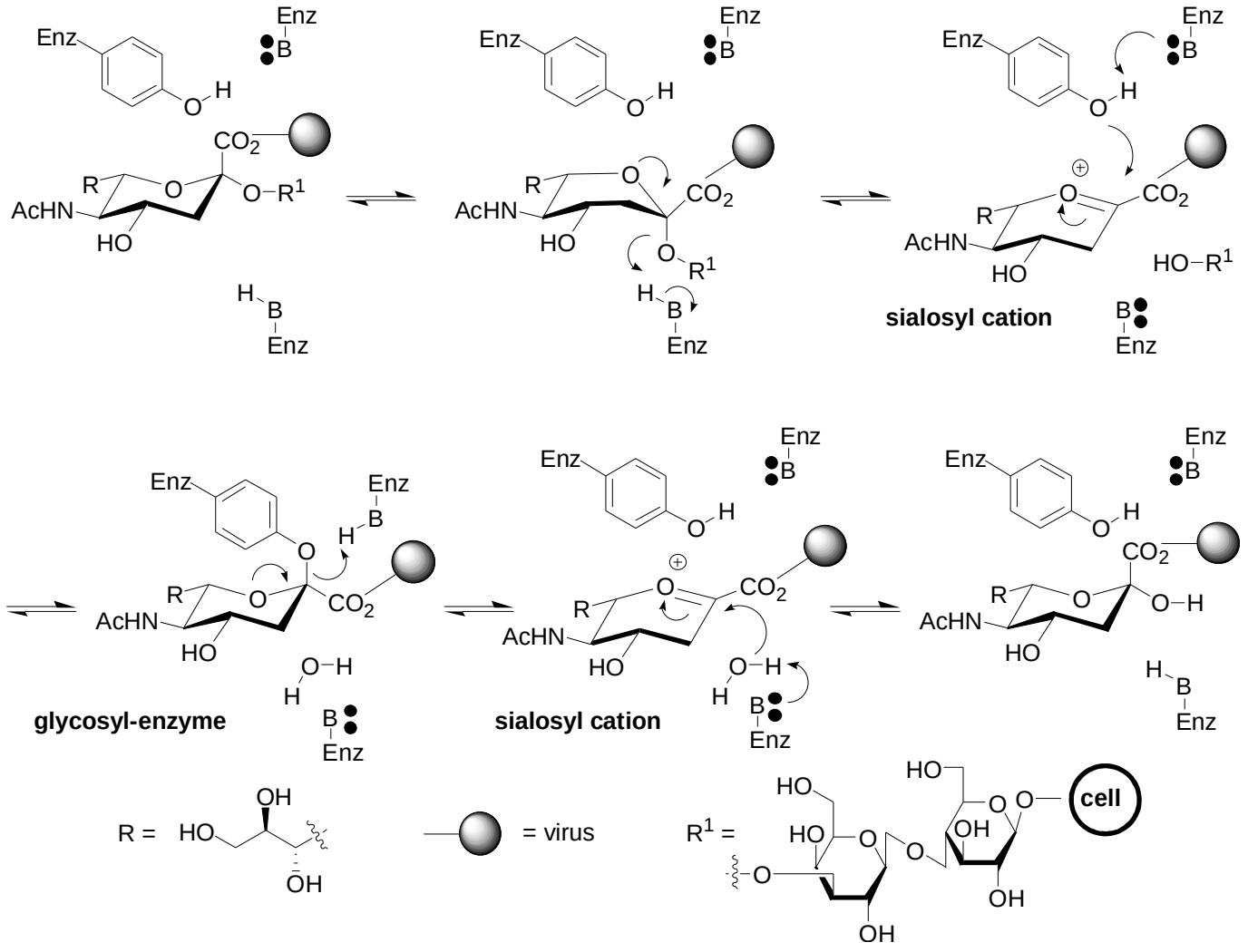
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Inhibition of the viral neuraminidase



SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Enzymatic mechanism of the viral neuraminidase



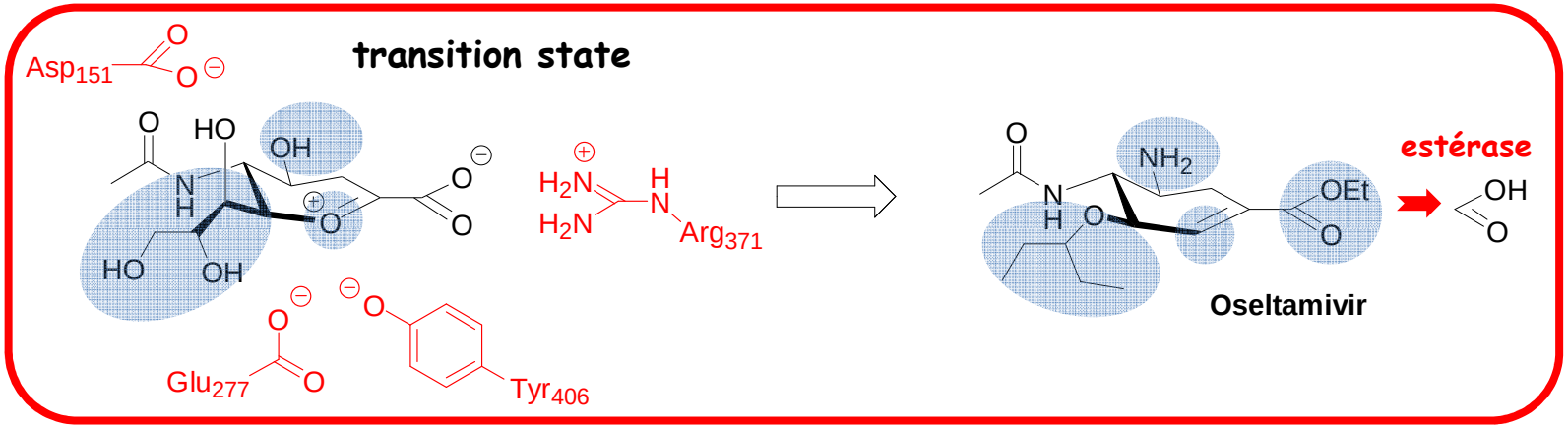
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

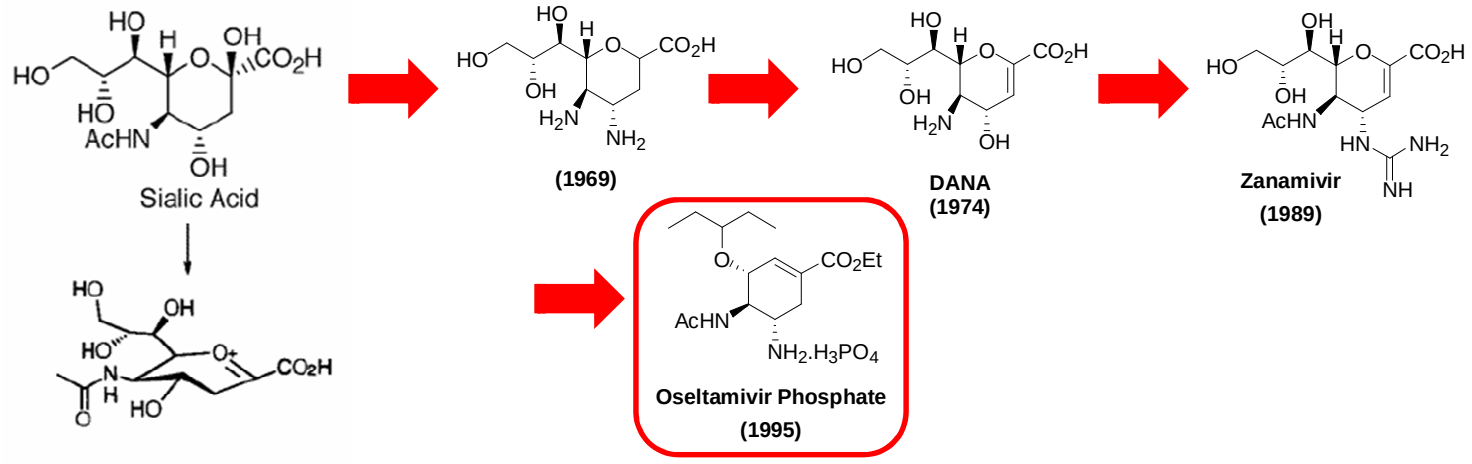
Oseltamivir : structure design

Goal of the design :

✓ establishment of a competitive inhibitor of the sialic acid

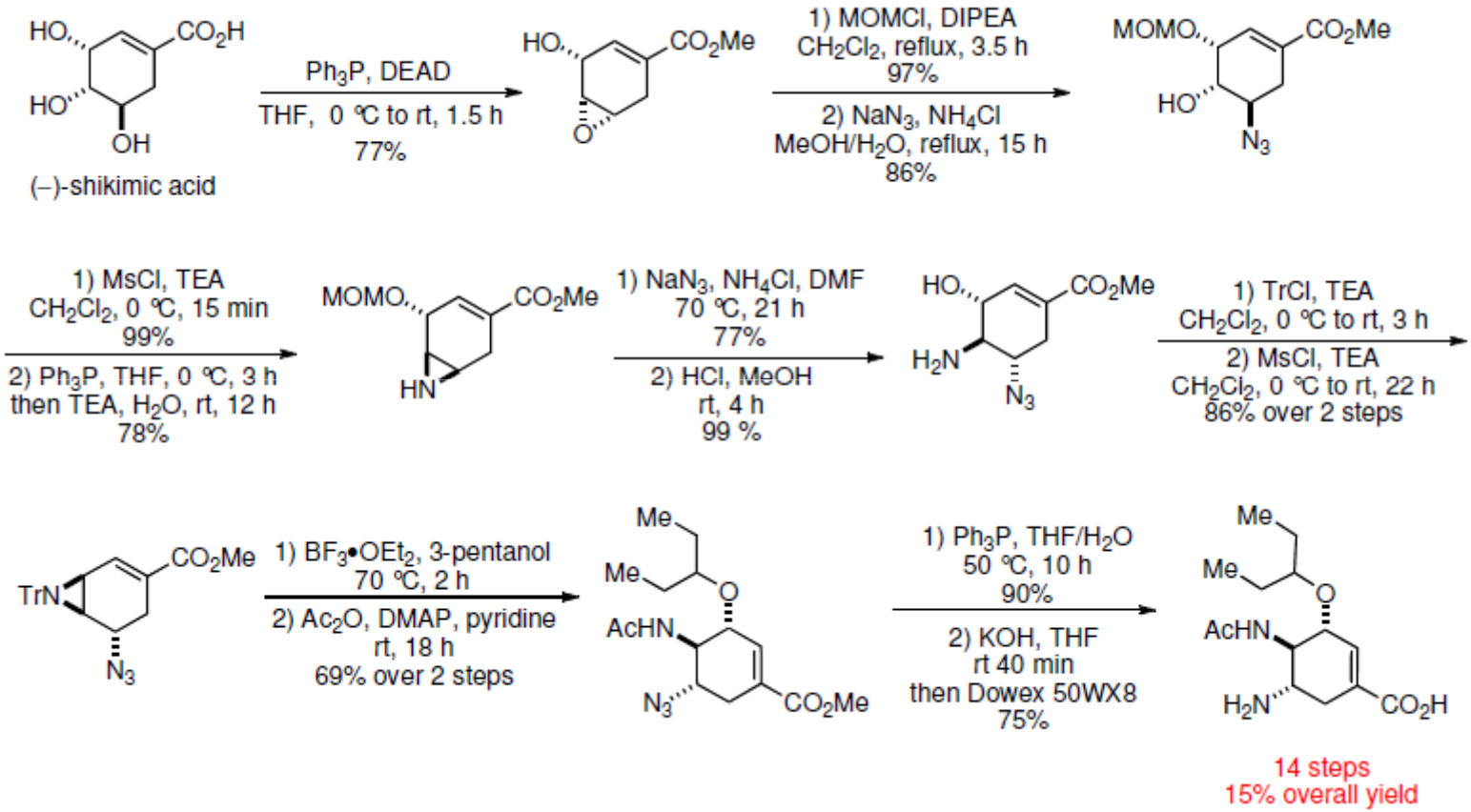
✓ preparation of an analogue of the transition state





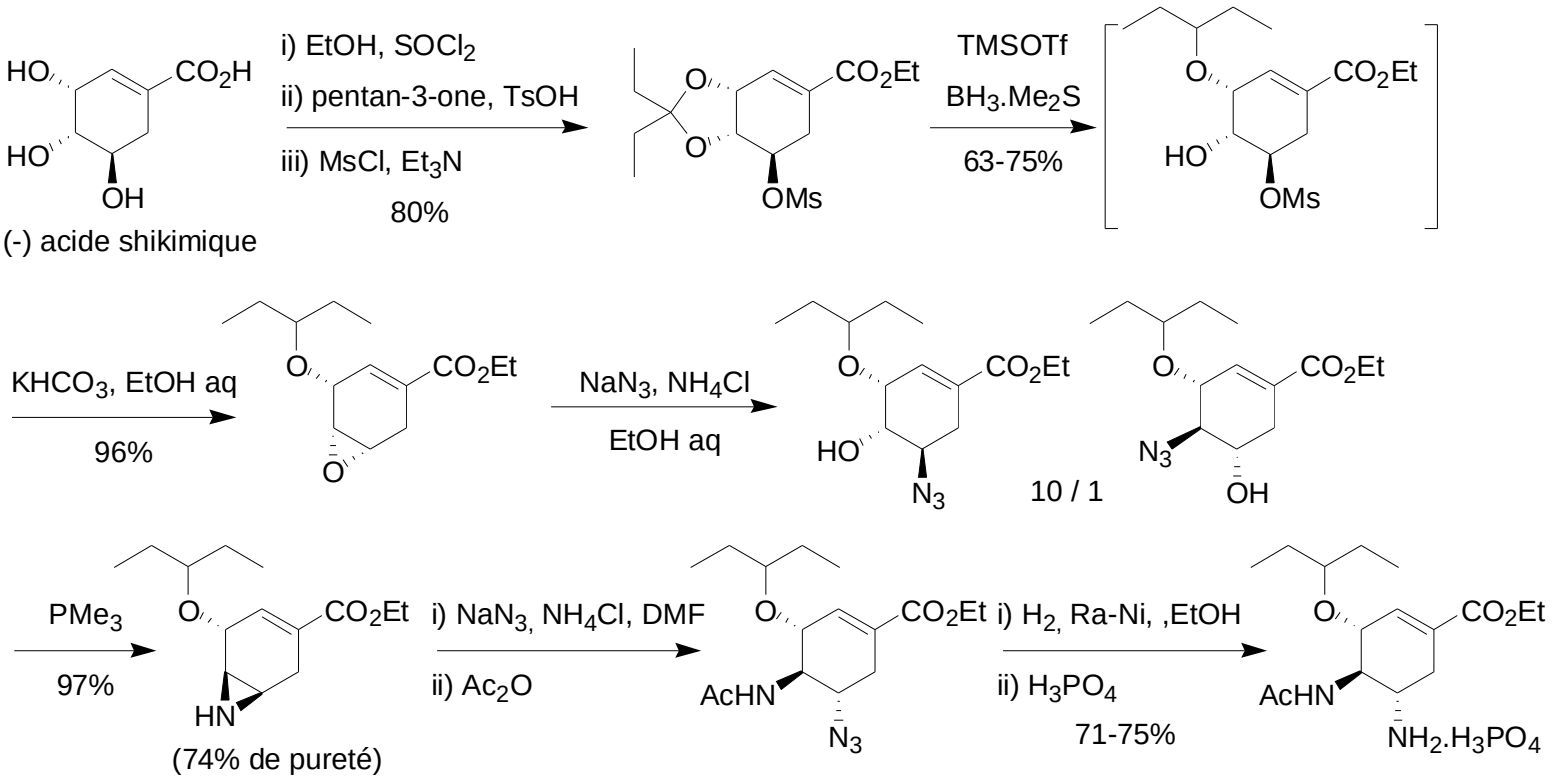
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Oseltamivir phosphate: the first synthesis



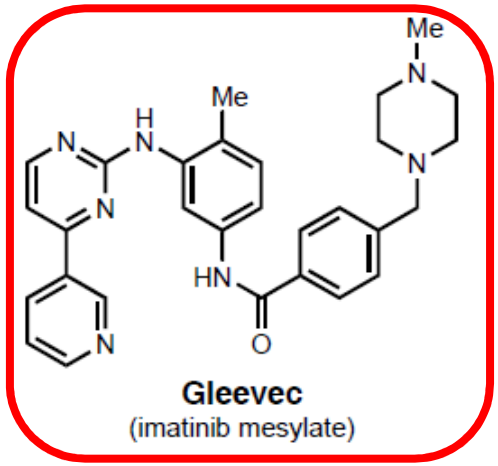
SYNTHESIS OF TAMIFLU (oseltamivir phosphate)

Oseltamivir phosphate: the Roche synthesis

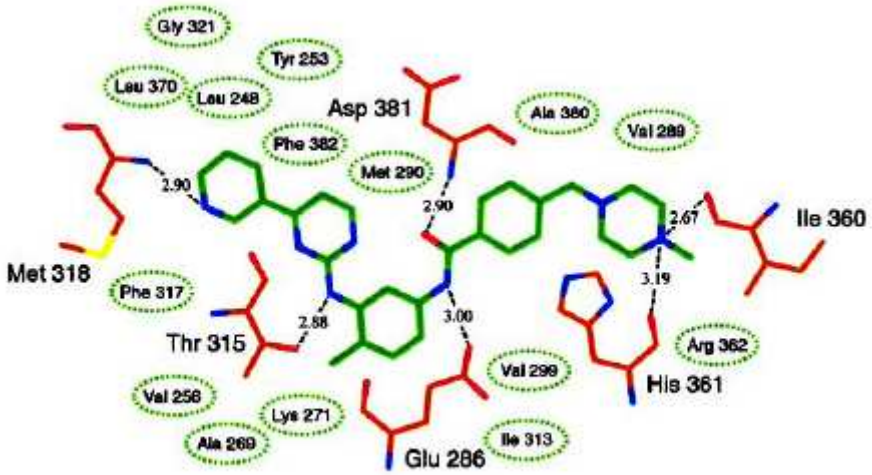


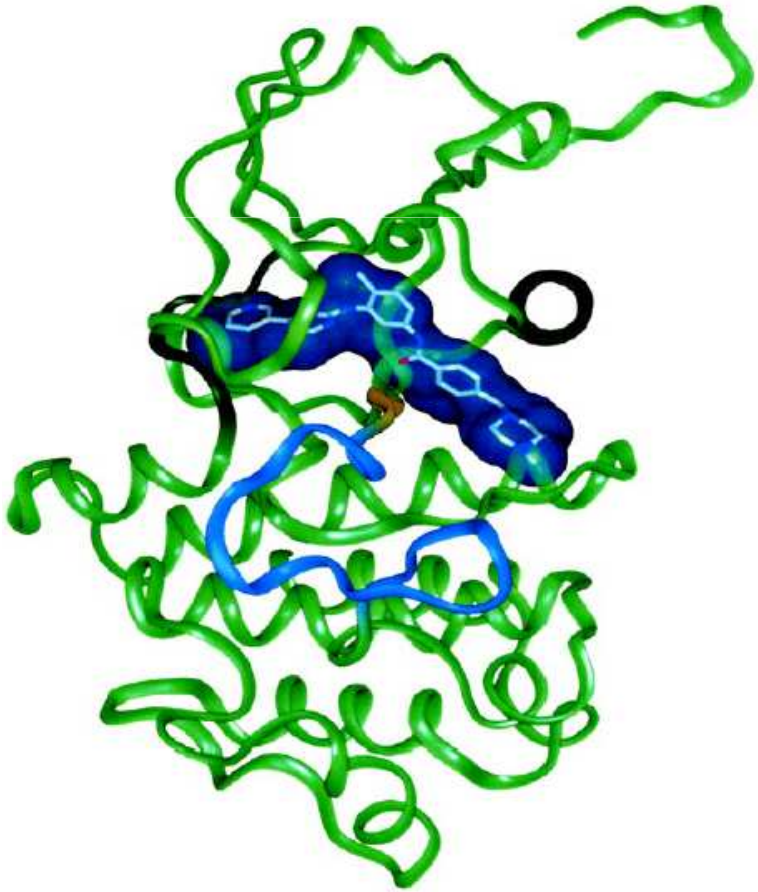
- 21% overall yield, 10 steps
- industrial synthesis
- minor drawback : the sourcing (shikimic acid)
- major drawback : the use of azide chemistry

SYNTHESIS OF GLIVEC (imatinib)



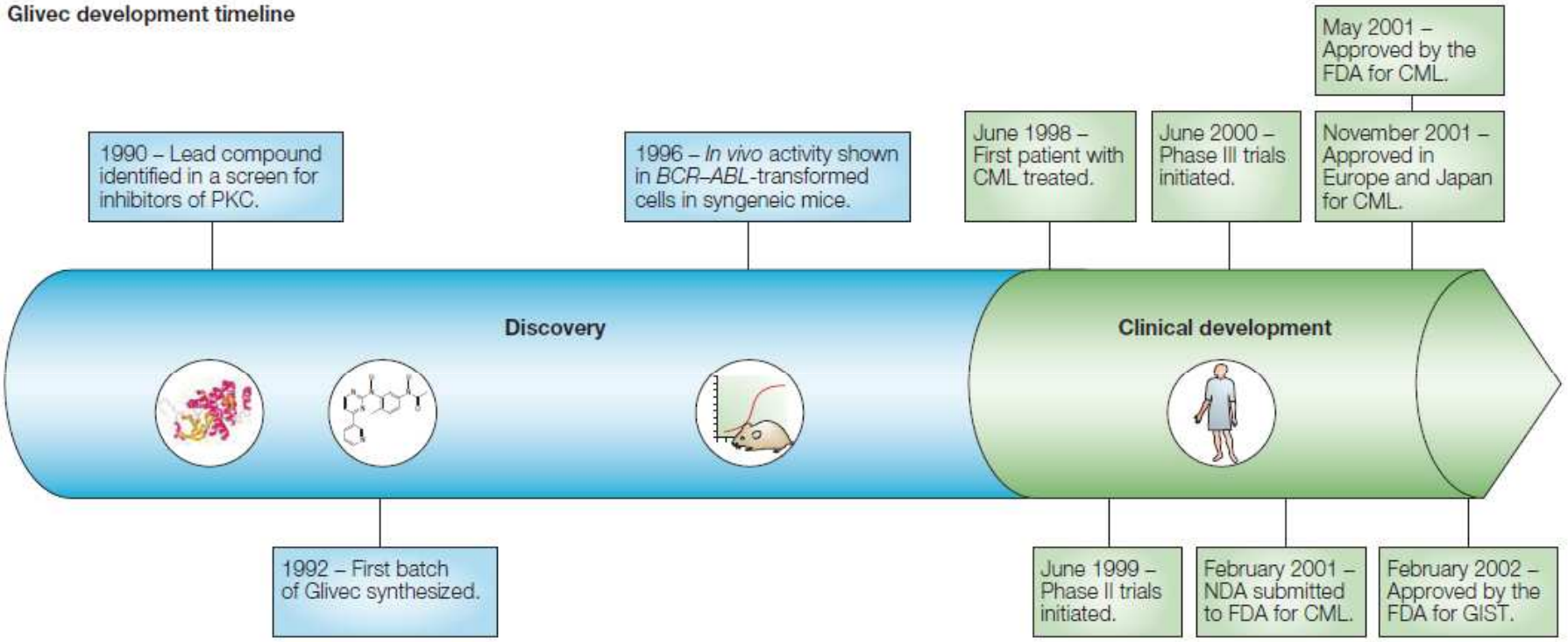
Novartis (2001)
Treatment of Chronic Myeloid Leukemia (CML)
First protein kinase inhibitor to reach the market
Selective inhibitor for a hybrid tyrosine kinase (Bcr-Abl)
Sales 2007 = $3 billion
Off patent in 2015

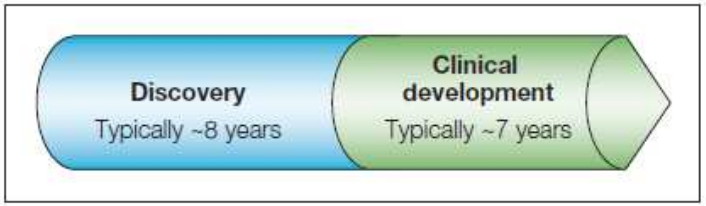




Cancer Res. ***2002,*** *62,* 4236.

SYNTHESIS OF GLIVEC (imatinib)





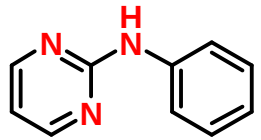
The clinical development was particularly rapid, as can be seen by comparison with the typical drug discovery and development times

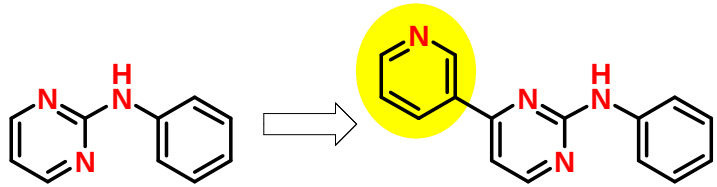
SYNTHESIS OF GLIVEC (imatinib)

Glivec : structure design

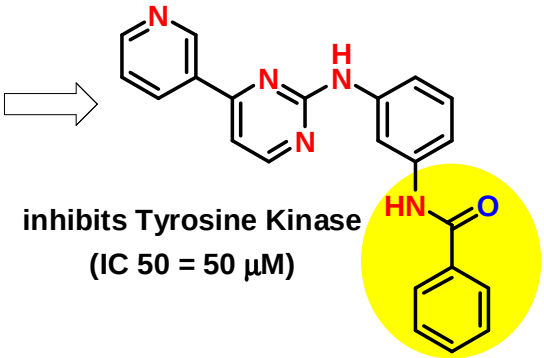
The phenylaminopyrimidine structure identified

- as Protein Kinase C (a serine-theonine kinase) inhibitor,
- by random screening of compound libraries.



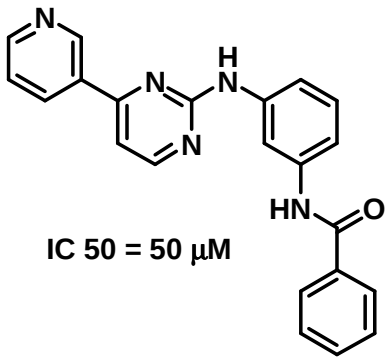


inhibition of PKC

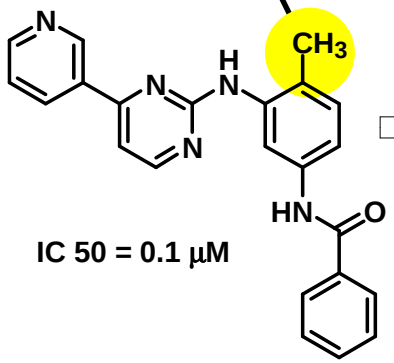


inhibits Tyrosine Kinase
(IC 50 = 50 μM)

Conformational blocker

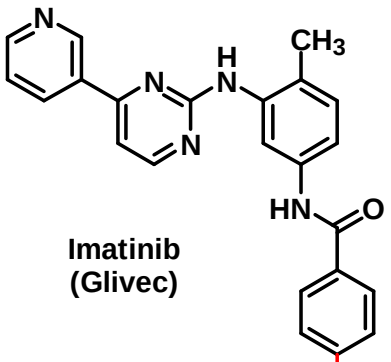


IC 50 = 50 μM

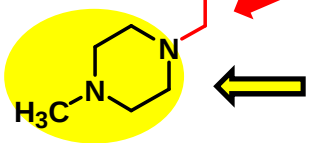


IC 50 = 0.1 μM

-increase activity *vs* tyrosine kinases
-no activity against serine-threonine kinases



Imatinib
(Glivec)

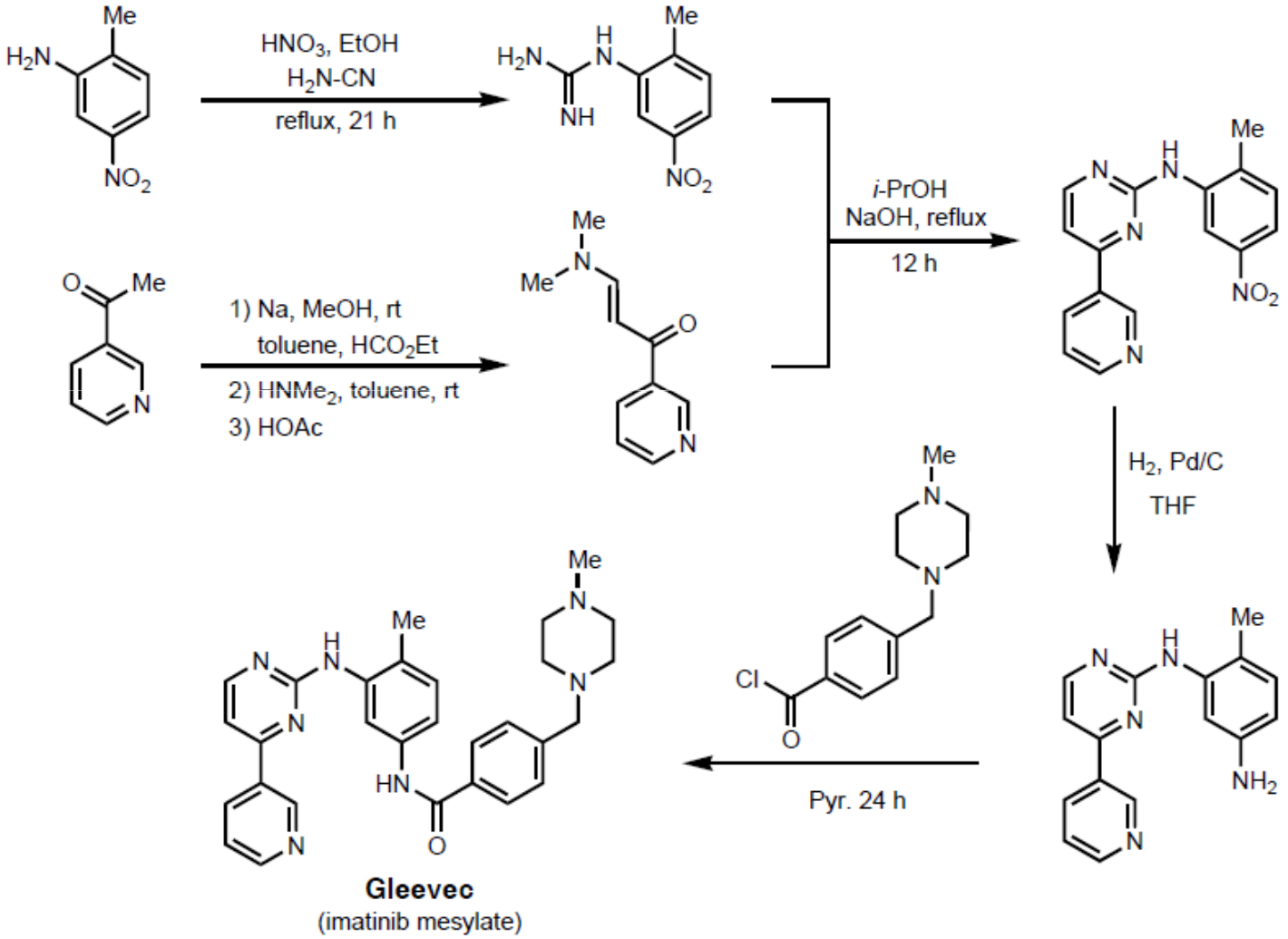


-spacer inserted to avoid aniline structure
-piperazine increases activity, selectivity and water solubility

Nature Review Drug Discovery. ***2002,*** *1,* 493.

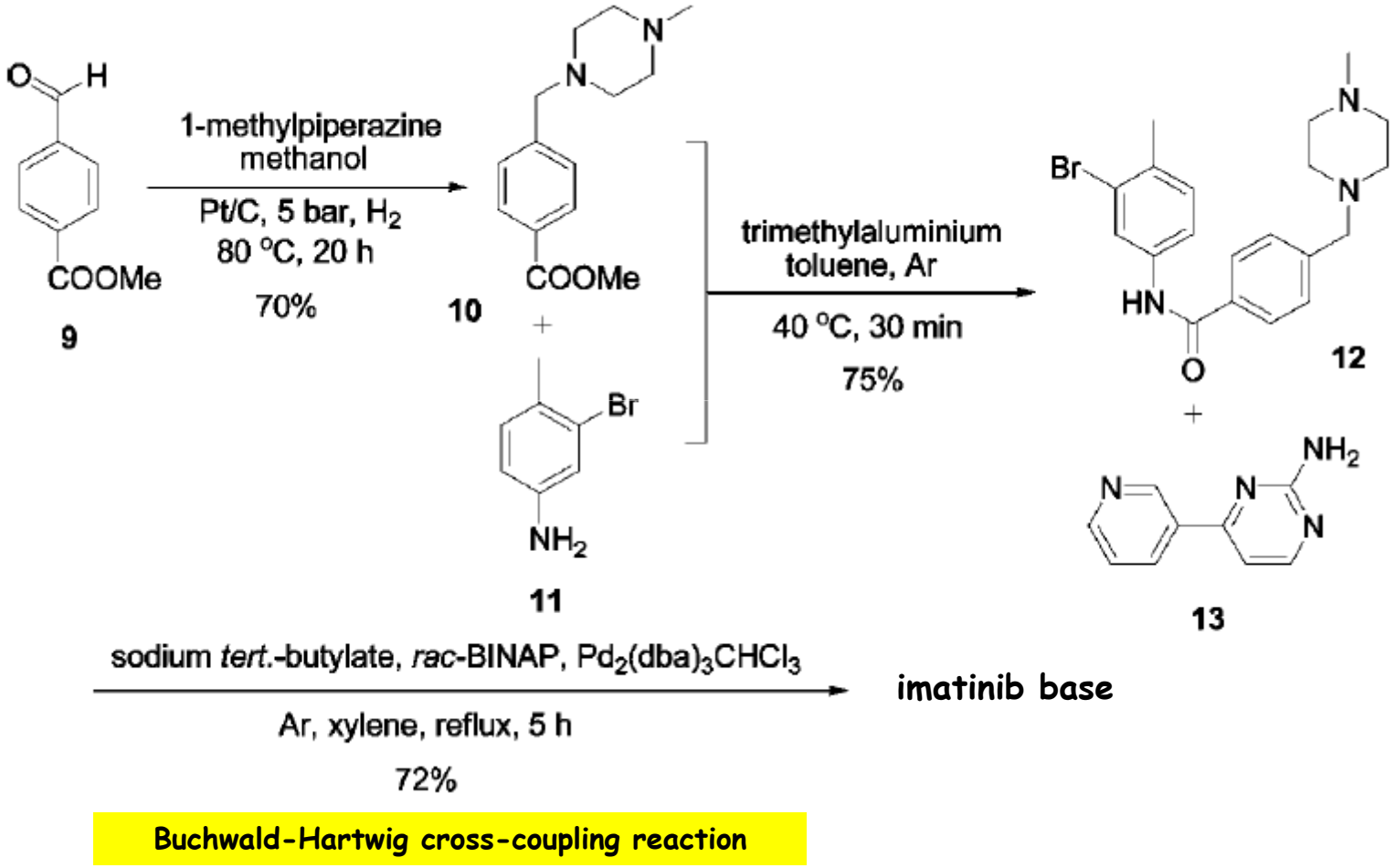
SYNTHESIS OF GLIVEC (imatinib)

Glivec : Zimmermann's route (1993)



SYNTHESIS OF GLIVEC (imatinib)

Glivec : Loiseleur's route (2003) – use cross-coupling reaction



Buchwald-Hartwig cross-coupling reaction