Synthetic Chemistry and Medicine

Kin Yang

"Has it ever occurred to you that medicinal chemists are just like compulsive gamblers: the next compound will be the real winner."

R. L. Clark at the 16th National Medicinal Chemistry Symposium, June, 1978.

Goal of talk: to provide a little understand on medicinal chemistry and relate it to applied synthetic chemistry

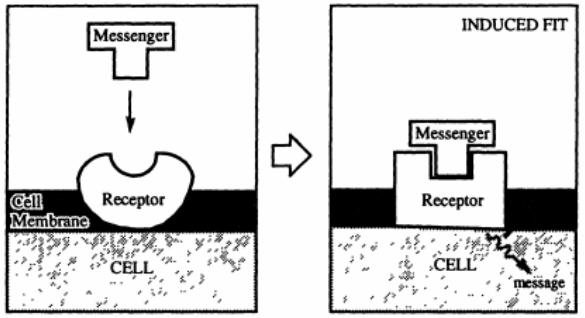
- Medicinal chemistry—a definition—*the use of synthetic organic chemistry to create molecules that will alter in a useful way some disease process in a living system. -D. Lednicer*

- Not unlike catalyst optimization with many more variables?

- Where do drugs come from? Both from natural sources and new entities from a bench.

- Method of Drug Discovery:
  Classical pharmacology (screening of chemicals to find biological)
  Reverse pharmacology (find chemicals based on biological target)

- Why do drugs work? Receptors.
  - Substrate must find and binds to target – lipids / proteins / nucleic acids
  - Binding due to non-covalent interactions.
  - Leads to biological response



Topics discussed

- Analgesics – Traditional to Modern Drug Design
- Selected Medicines
  - Antihistamines
  - Antivirals
  - Antidepressant
  - Antifungal

Opioids – alkaloids derived from opium (poppy)

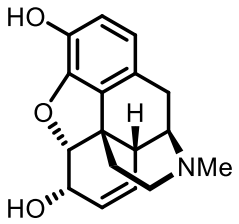
-One of the oldest fields in medicinal chemistry, yet one where true success is yet to be found

-Perhaps oldest known drug with recording use dating back 2000 years in china.

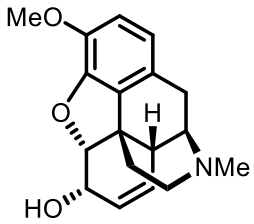
-**Analgesic effects** “detachment from pain” + euphoric properties lead to severe dependence of the drug.

-Total alkaloid content of opium is ~5–10%.

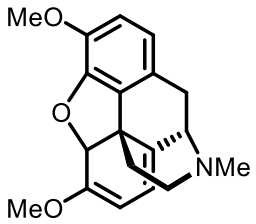
Major constituents:



morphine
7–17%



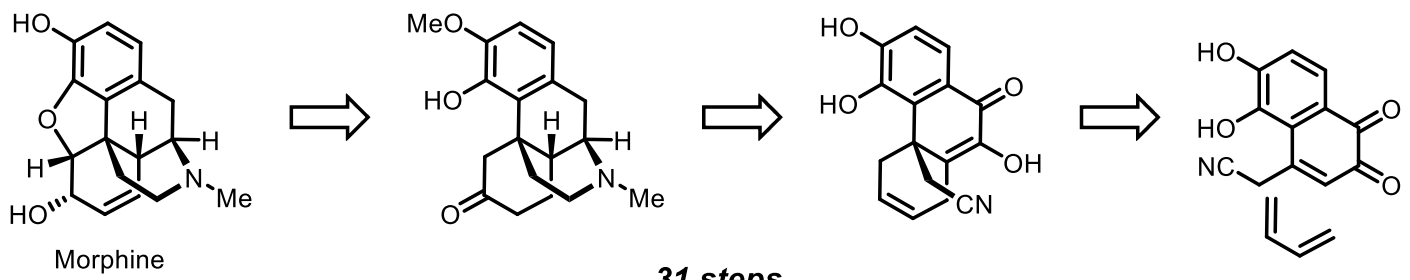
codeine
2–4%



thebaine
1–3%

- Pure morphine isolated 1803 - functional group determination 1881
- structure determination 1925 - first total synthesis 1952

First total synthesis of Morphine by Gates. JACS 1953, 4340



Morphine

31 steps
0.06% overall yield

Other syntheses:

Rice 1980	Overman 1993	Cheng 2000	Guillou 2008
Evans 1982	Mulzer 1996	Ogasawara 2001	Magnus 2009
Fuchs 1988	Parsons 1996	Taber 2002	Stork 2009
Tius 1992	White 1997	Trost 2002	Fukuyama 2010
Parker 1992	Hudlicky 1998	Michels 2005	+ More...

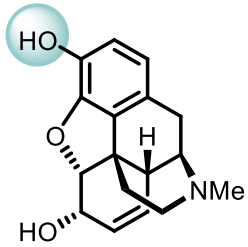
Morphine obtained by fractionation of opium.
Projected opium production in Afghanistan 6,400 metric tons or **6,400,000 kg** (2014)

Goal: Eliminate side effects while retaining activity.

Traditional approach: Trial and error.

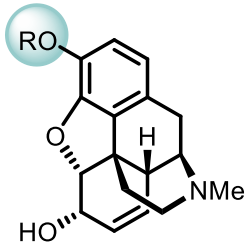
1. Identification of drug molecule with biological response (poppy plant)
2. Synthesis enables testing of Structure-activity relationships – see which parts responsible for function
3. Drug development – synthesize analogs to improve activity and reduce side effects
4. Propose theories on mechanism of action.

What happens when we modify functional groups? (many studies done prior to knowledge of full structure)
(Morphine functional groups determined by 1881)

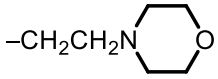


morphine

alkylation

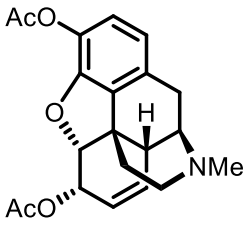


R= Me ***codeine*** (~20% strength of morphine)
Et ***ethylmorphine*** (used in ophthalmology)
Ac ***acetylmorphine***
} metabolized to morphine



pholcodine
(Cough suppresant)

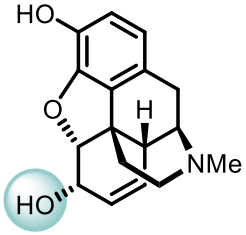
Leads to weakining or loss of analgesic effect
Free phenol essential for function



heroin

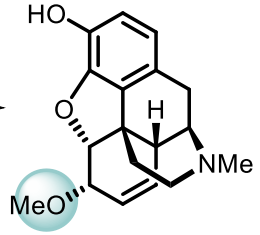
2x activity of morphine

Ac_2O



morphine

KH (9 equiv.)
MeI (1.1 equiv.)

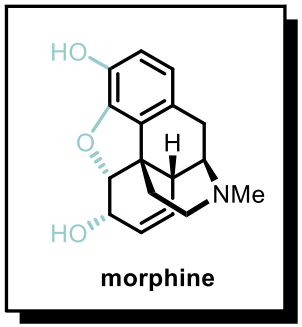


heterocodiene

5x activity of morphine

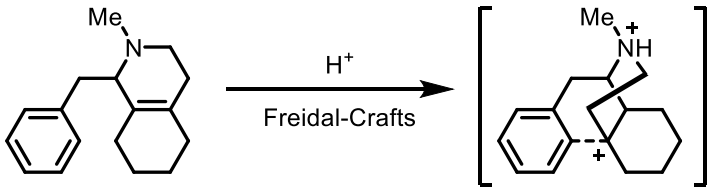
Due to superior pharmacodyanamic properties rather than higher receptor affinity.
Easier to cross Blood-brain barrier - Greater drug bioavailability

Simplification of Structure



morphine

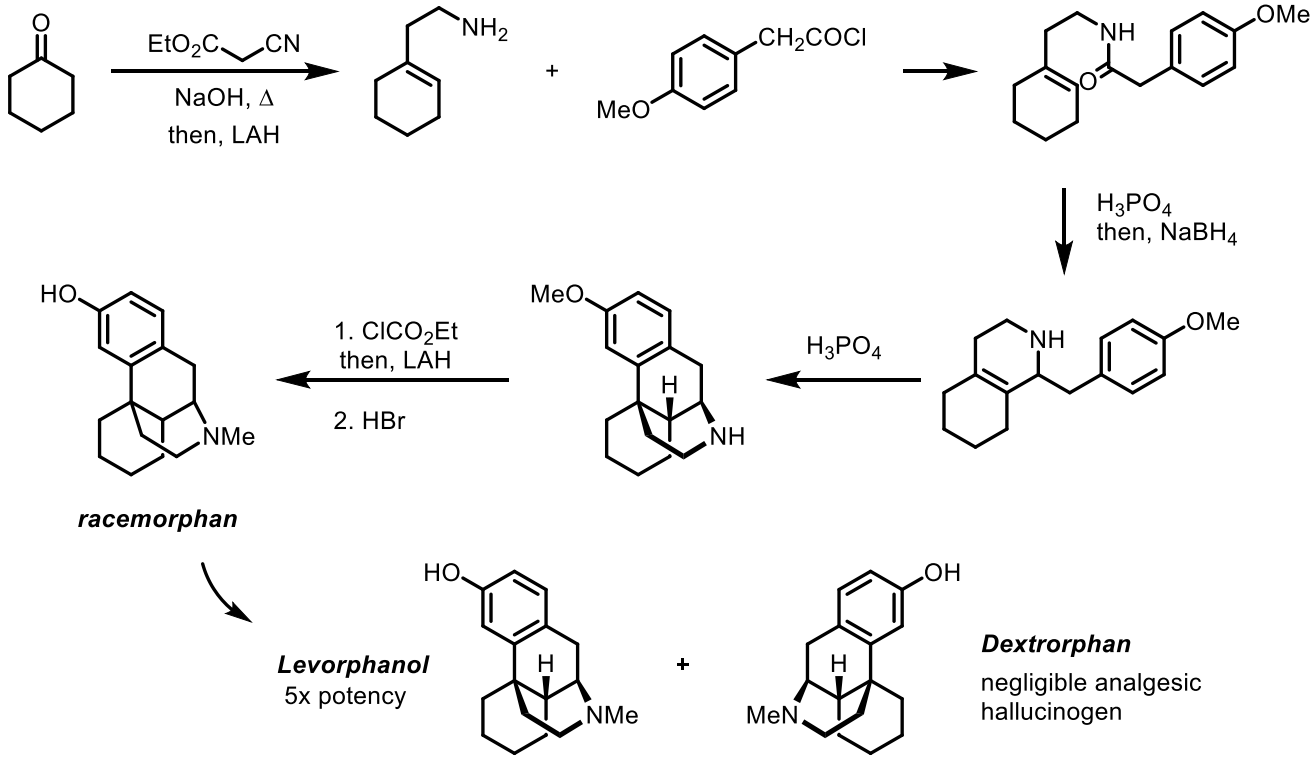
Grewe and Mondon Chem. Ber. 81, 279, 1948



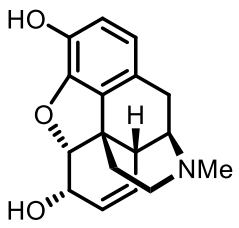
bare morphine skeleton

Can we retain function with simpler structure?

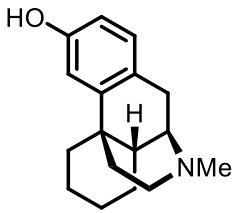
A commercial route: Schnider Helv. Chim. Acta. 1956, 429



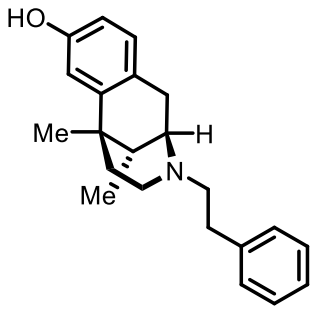
Further Simplification of Structure



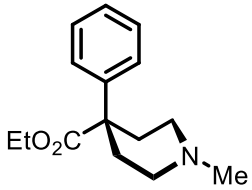
morphine



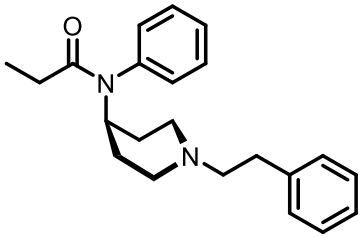
Levorphanol
5x potency



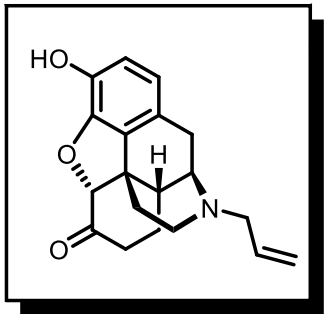
Phenazocene
4x potency



Pethidine
0.2x potency



Fentanyl
100x potency



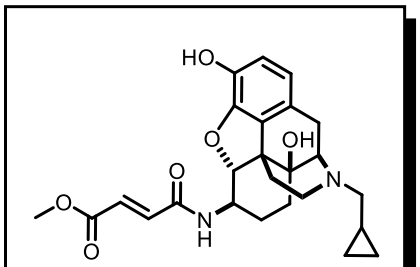
Naxolone
opioid antagonist
used for cases of opioid overdose

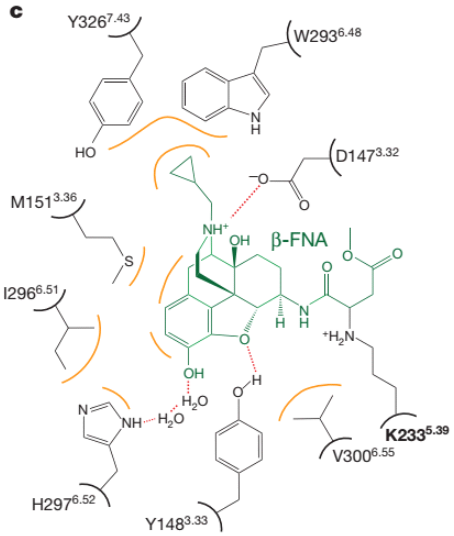
Identification of receptor site can allow for rational design

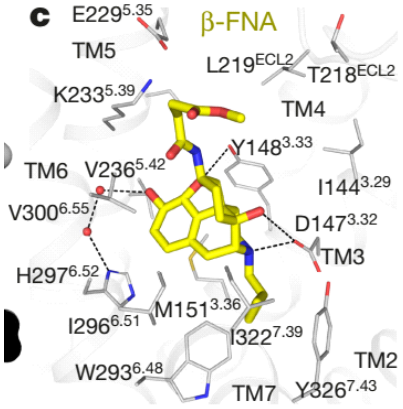
Use of H^3-Naxolone led to identification of opiod receptors in mammalian brain.
Multiple receptors (δ,κ,μ) on peripheral sensory neurons.
Each receptor responsible for multiple functions. (anagesia, sedation, dependence, etc.)
μ Opioid receptor particular important - trigger for analgesia and also side effects

Pert CB, Snyder SH *Science.* **1973.** 1011.

Crystal structure incorporating the opioid allows for better understanding of structural basis for μ-Opioid receptor function







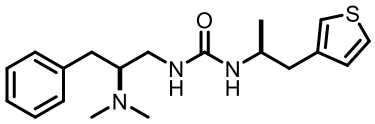
Alanine	Ala	A
Cysteine	Cys	C
Aspartic Acid	Asp	D
Glutamic Acid	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
Asparagine	Asn	N
Proline	Pro	P
Glutamine	Gln	Q
Arginine	Arg	R
Serine	Ser	S
Threonine	Thr	T
Valine	Val	V
Tryptophan	Trp	W
Tyrosine	Tyr	Y

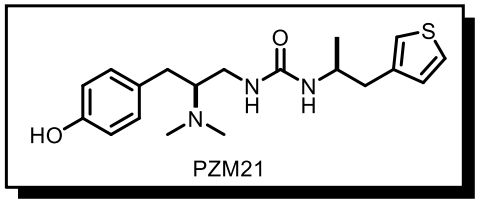
Structure-based discovery

Crystal structure as basis, computationally dock libraries of molecules into μ-OR pocket.

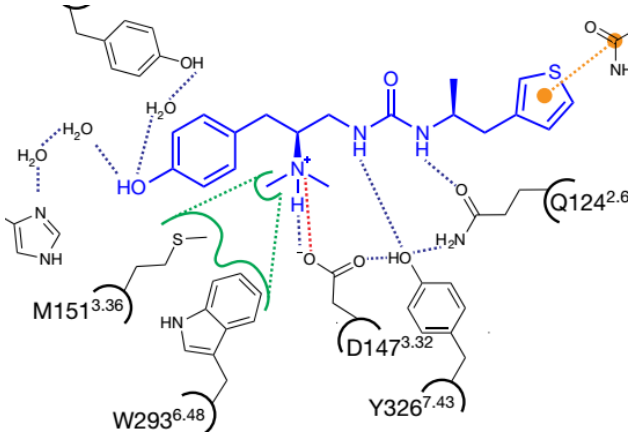
3 million available lead-like compounds, average of 1.3 million configurations evaluated for each.

Manually examined the top 2,500 (0.08%) - Ultimately settled on screening 23 high-scoring molecules


best initial compound


PZM21

PZM21 is less potent (0.25x) than morphine
yet has very low β-aresstin-2 recruitment (protein responsible for undesired effects)



doi:10.1038/nature19112
Manglik Nature Aug 17, 2016

Histamines and Anti-histamines

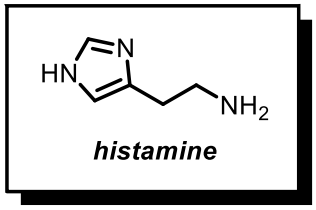
Histamine is released from mast cells (White blood cell) in event of:
Tissue injury or introduction of foreign substance.

Histamine binds to protein known as Histamine H_1 Receptor - leads immune response and undesireable symptoms

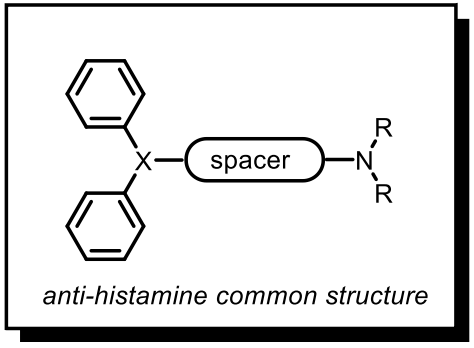
Anti-histamines are drugs that reduce or eliminate the effects by histamine

Mechanism of action:

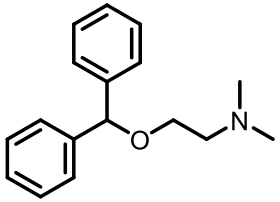
- -Bind H_1 receptor thus inhibit histamine binding
- -Displaces histamine from receptor H_1 receptor
- -Generally most beneficial when given early



histamine



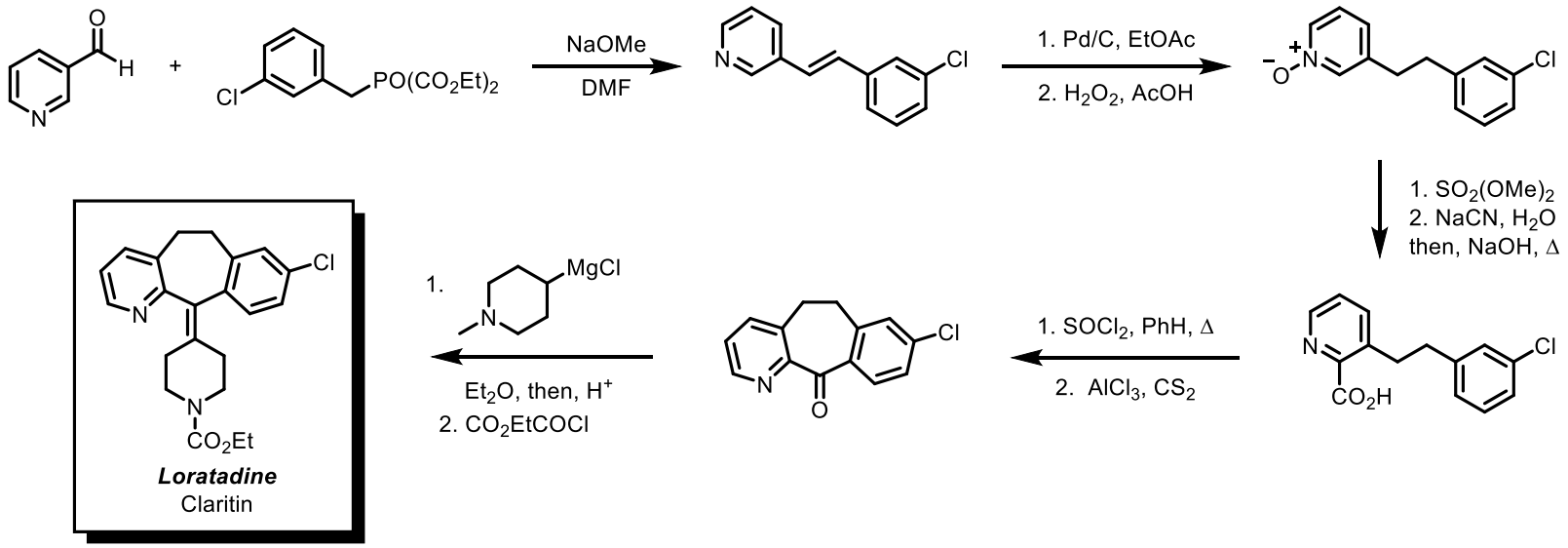
anti-histamine common structure



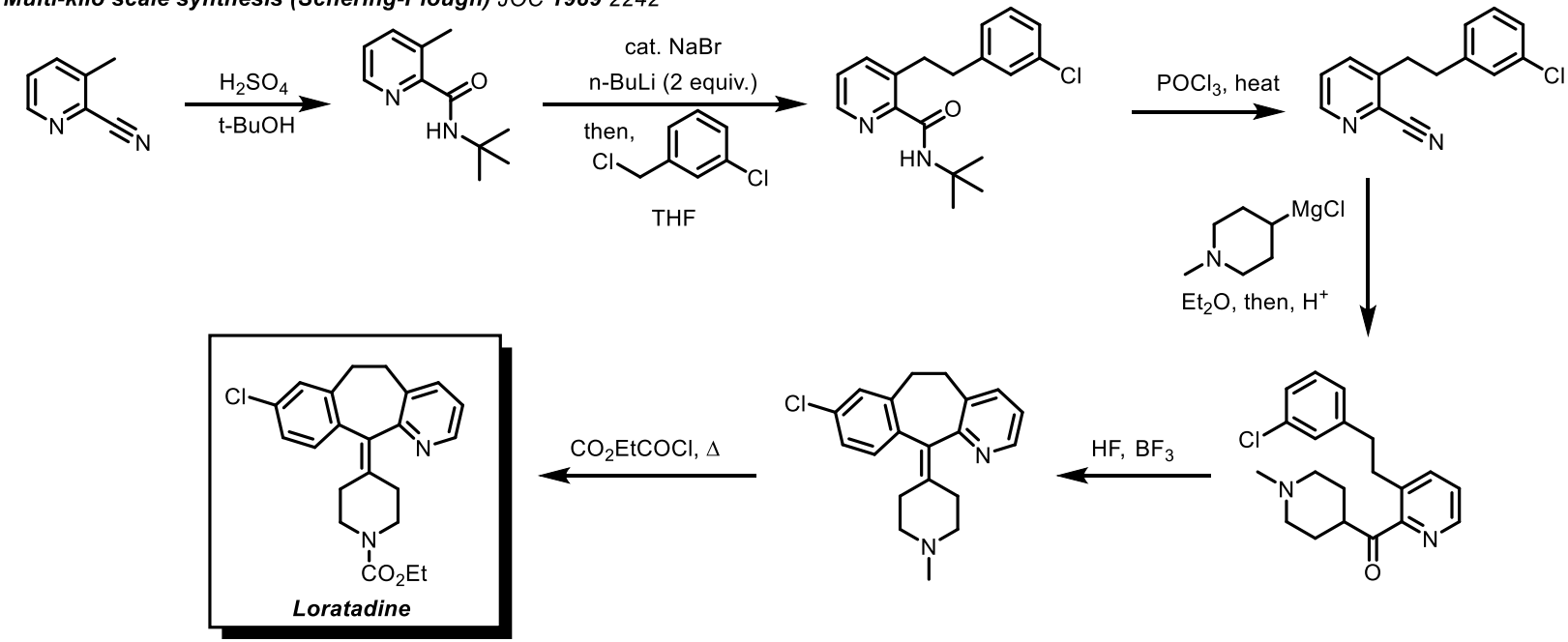
anti-histamine

diphenhydramine
discovered 1943

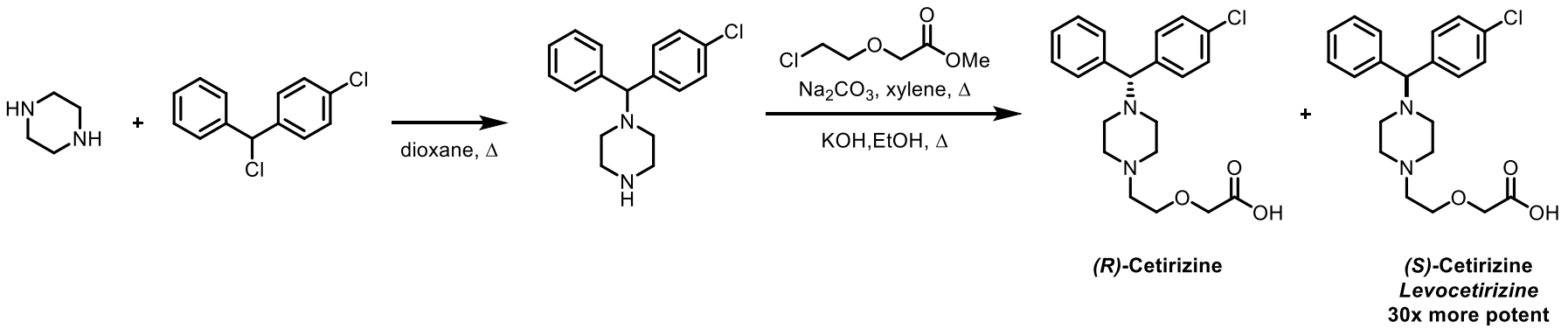
Early Route to Loratadine *Schering Corporation Patent: US 4282233 (1981)*



Multi-kilo scale synthesis (Schering-Plough) *JOC* ***1989*** *2242*



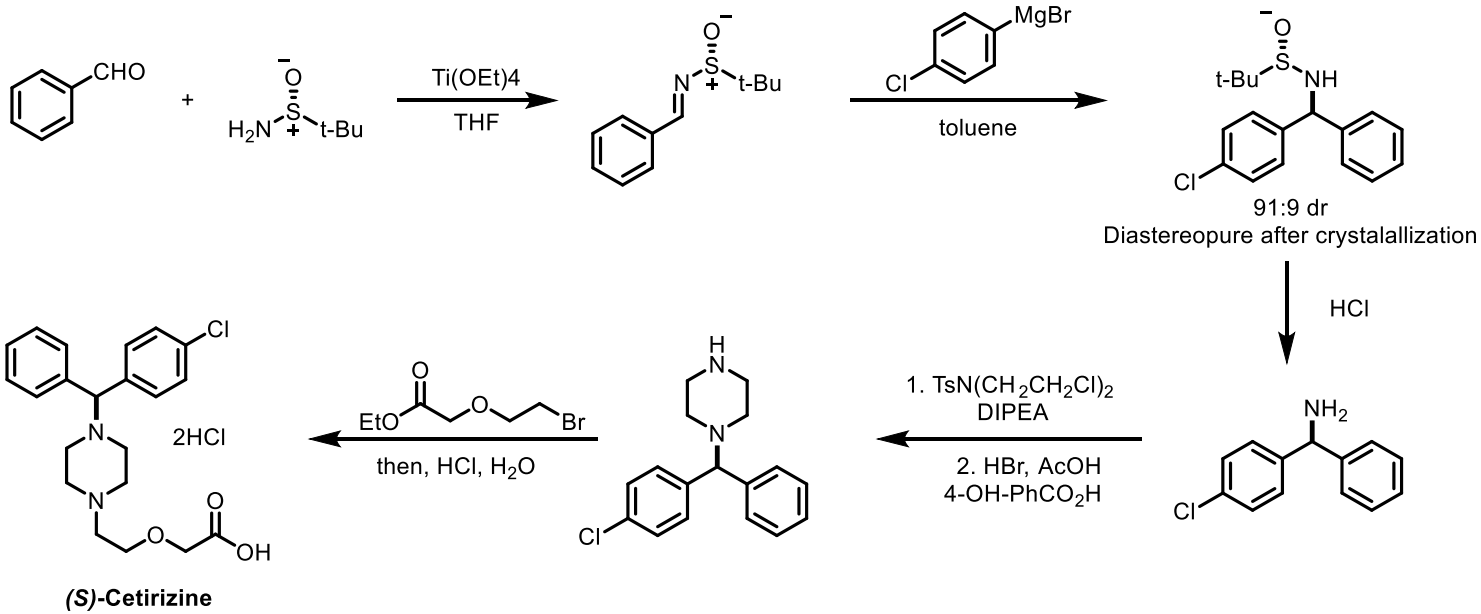
Early route to Ceterizine (Zyrtec): Ucb Pharmaceuticals Parent: US 4525358 (1985)



***(R)*-Cetirizine**

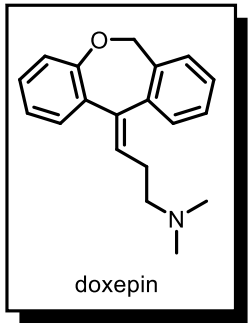
***(S)*-Cetirizine**
Levocetirizine
30x more potent

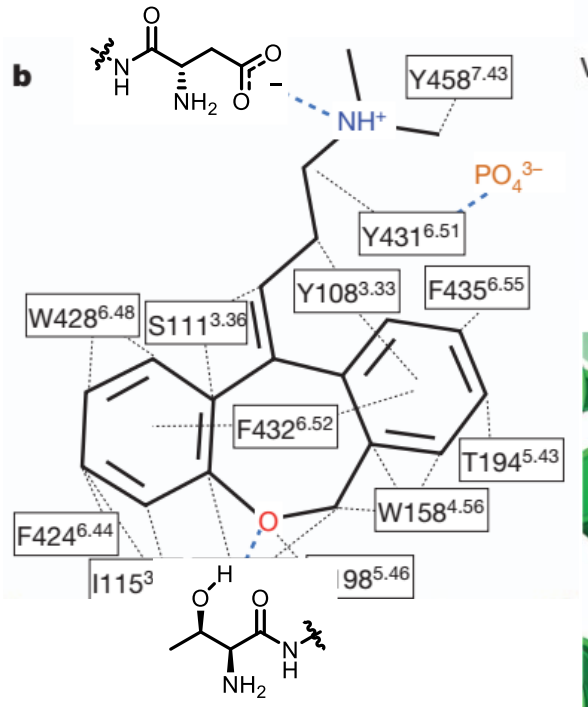
Scalable route to *(S)*-Cetirizine: Sepracor TL, 2002, 923 (C. Senanayake)

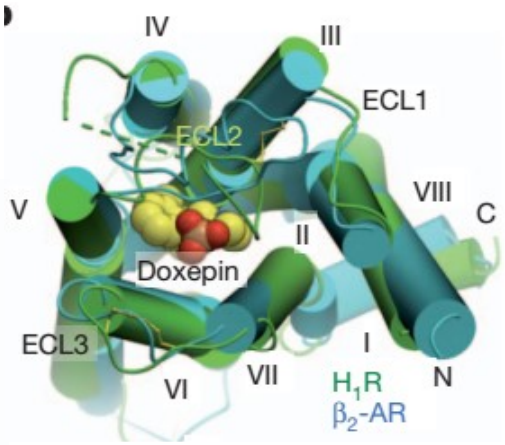


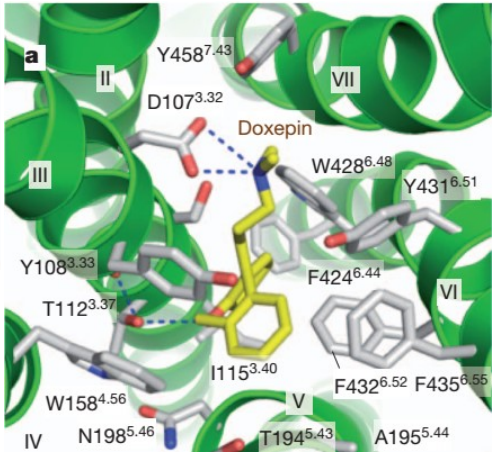
***(S)*-Cetirizine**

Crystal Structure of the histamine H_1 receptor complex with doxepin









Alanine	Ala	A
Cysteine	Cys	C
Aspartic Acid	Asp	D
Glutamic Acid	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
Asparagine	Asn	N
Proline	Pro	P
Glutamine	Gln	Q
Arginine	Arg	R
Serine	Ser	S
Threonine	Thr	T
Valine	Val	V
Tryptophan	Trp	W
Tyrosine	Tyr	Y

R. Stevens and S. Iwata *Nature* 2011 65-70

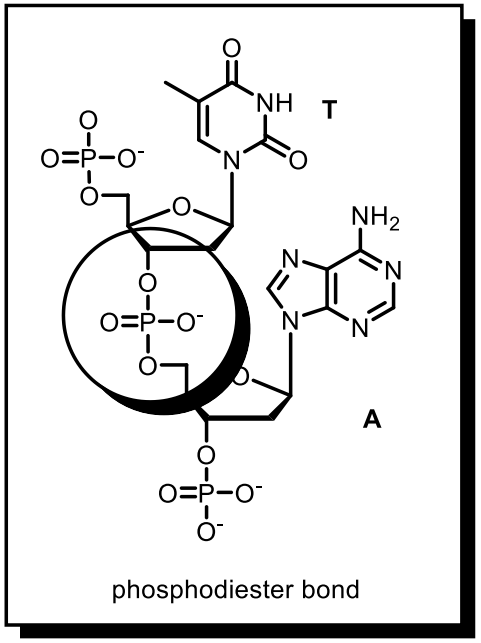
Anti-virals

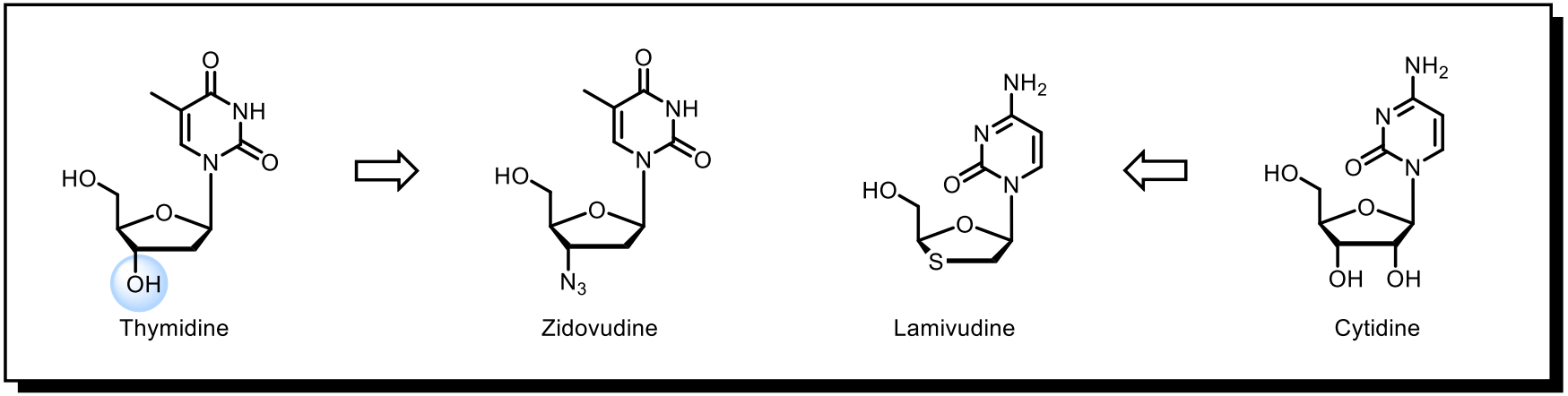
Nucleoside analog reverse-transcriptase inhibitors (NRTIs) minic nucleosides.

Zidovudine (AZT) is a HIV reverse transcriptase inhibitor and is a analog of thymidine.
Upon phosphorylation, competes for incorporation into viral DNA, terminating DNA synthesis.

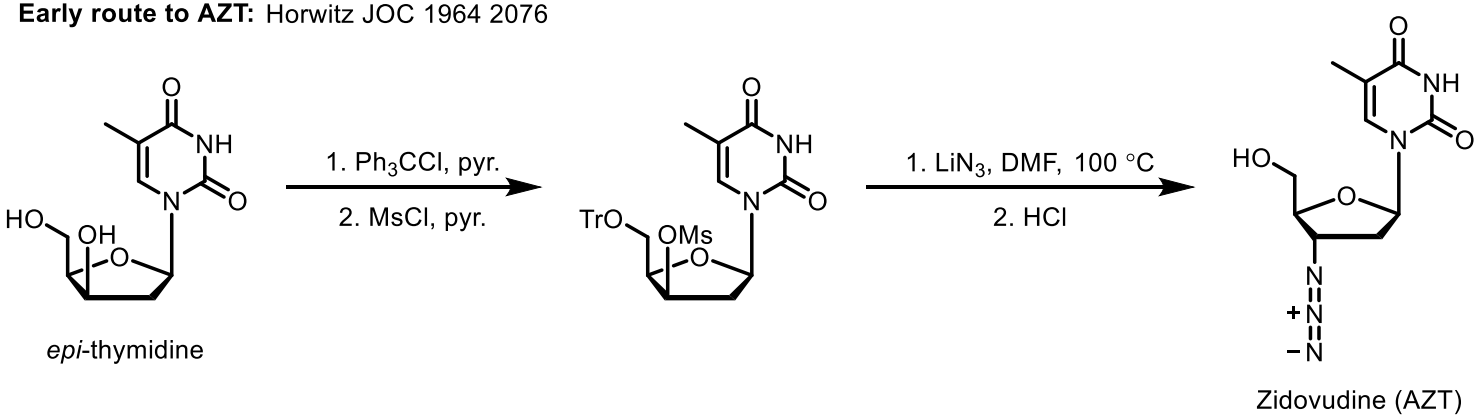
Lamivudine is an analog of cytidine.
A reverse transcriptase inhibitor in for HIV and hepatitis B virus.

The lack of a 3'-OH group in the nucleoside mimic prevents the formation of the
5' to 3' phosphodiester linkage essential for DNA chain elongation.

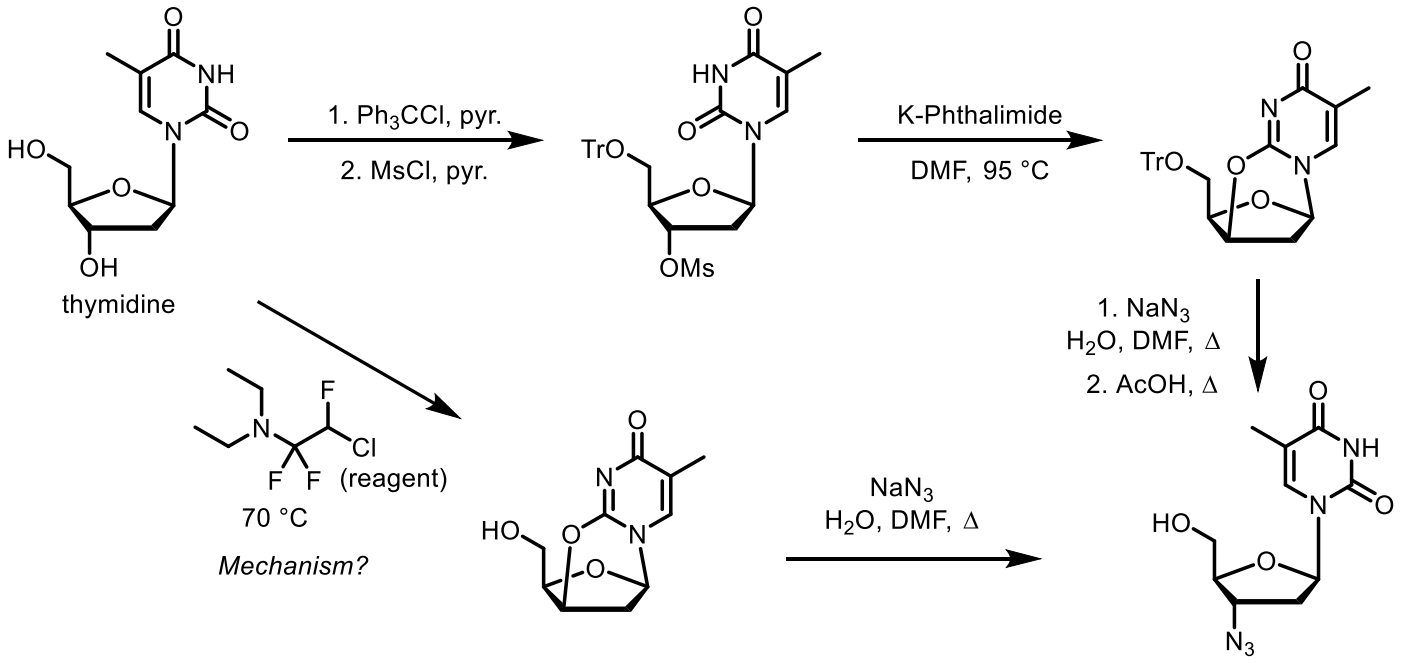




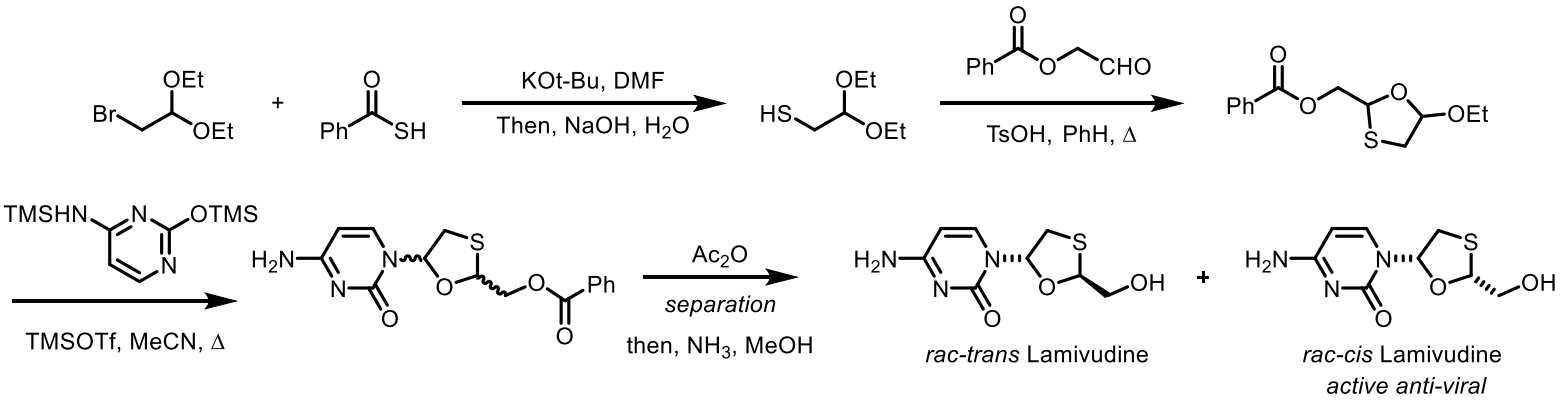
Early route to AZT: Horwitz JOC 1964 2076



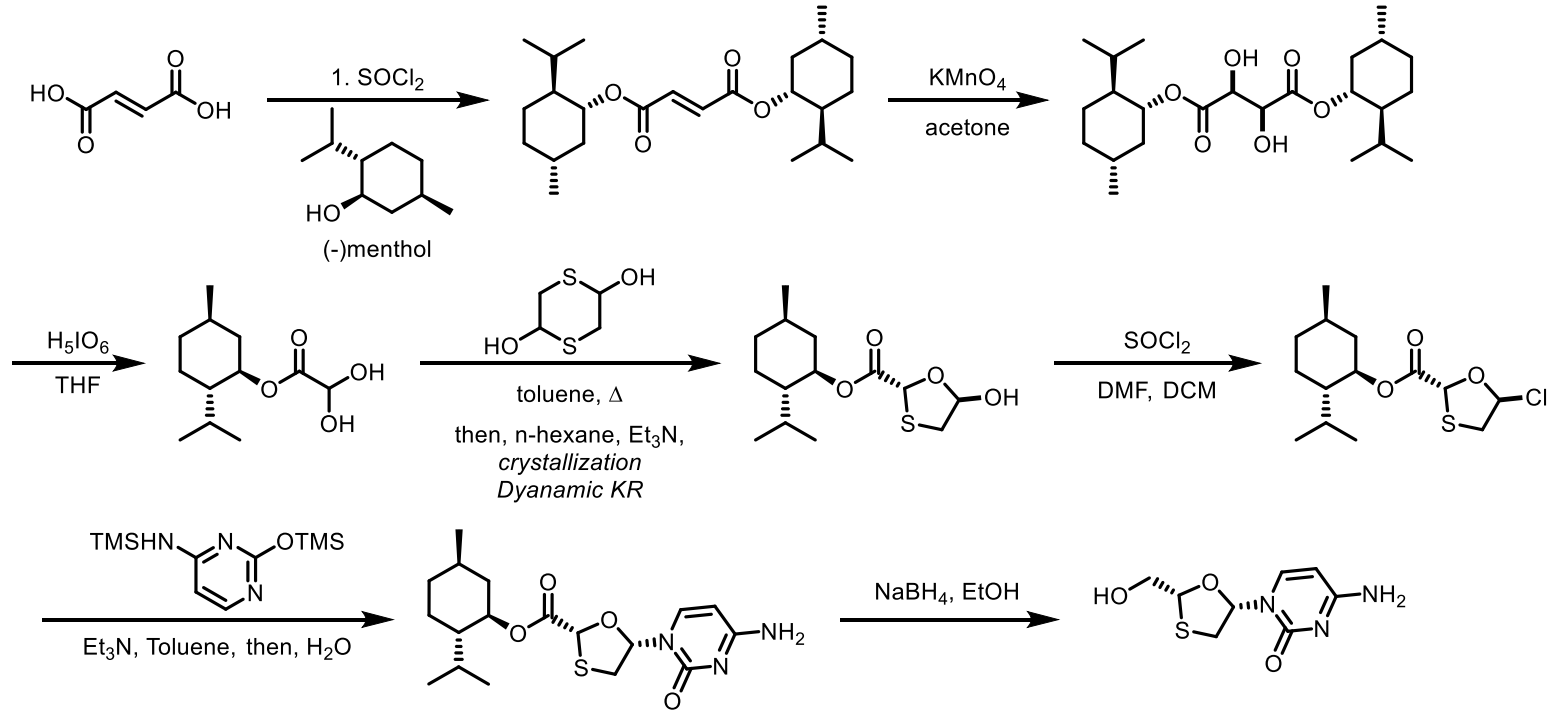
Updated route from thymidine: Glinksli JOC 1973 4299



Early approach for synthesis of Lamivudine: Iaf Biochem International, Inc. Patent: US5047407 (1991)



Enantioselective synthesis of Lamivudine (GSK) TL 2005 46 8535

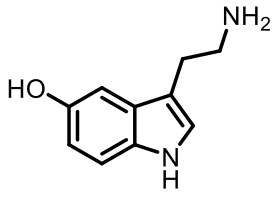


Mechanism of Anti-depressants

- **monoamine hypothesis of depression** hypothesizes the basis of depression due to a depletion of serotonin and/or other neurotransmitter at synaptic cleft.

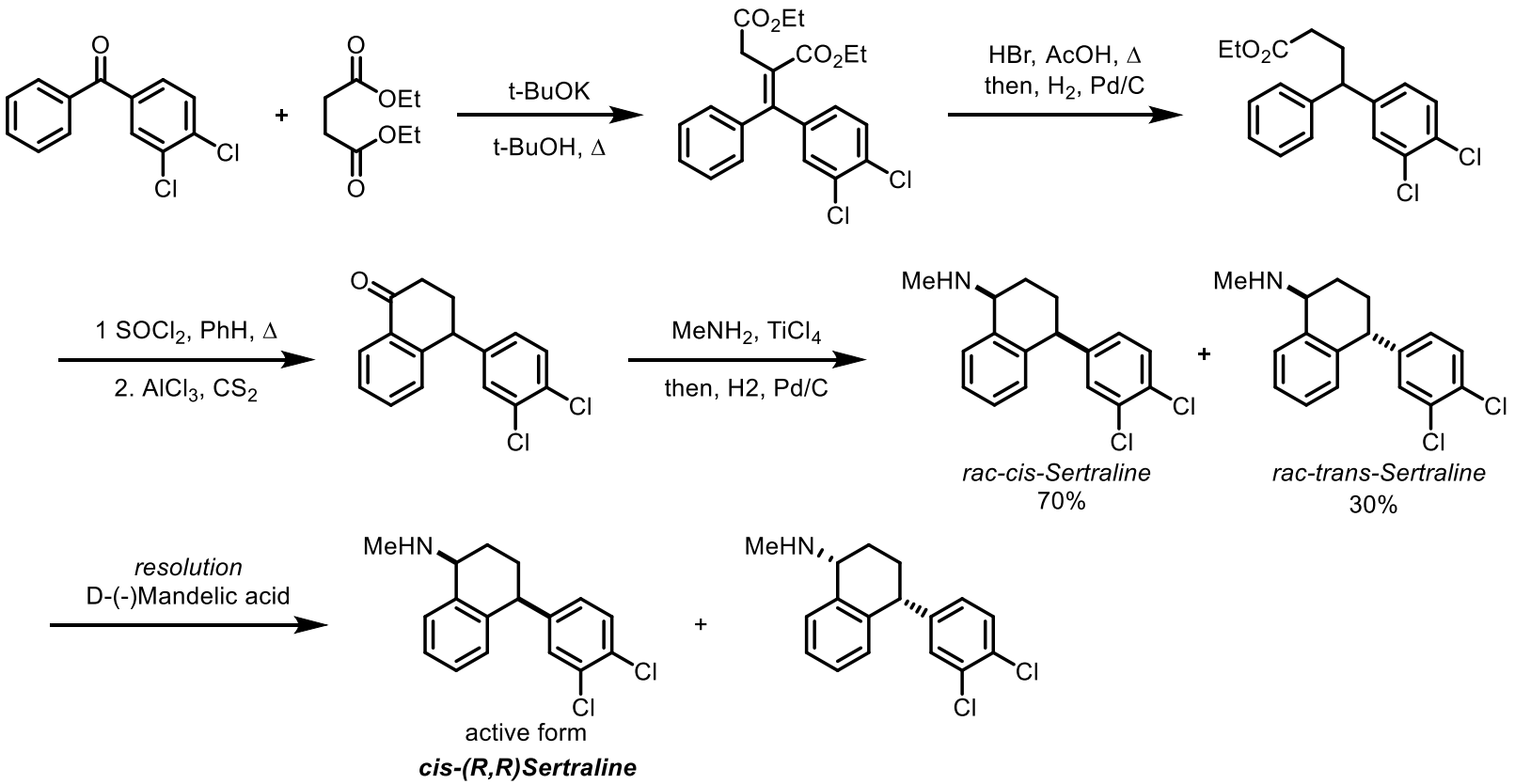
- The **Serotonin transporter is responsible** for re-uptate of serotonin. If blocked by a foreign chemical **(Selective serotonin reuptake inhibitor (SSRI))** leads to greater serotonin concentration.

- **5-HT$_{1A}$** receptor that inhibits firing of serotonergic neurons. After a few weeks, of **chronic overstimulation**, **5-HT$_{1A}$ receptor becomes subsensitive** due to and is **downregulated** – leading to therapeutic effects.

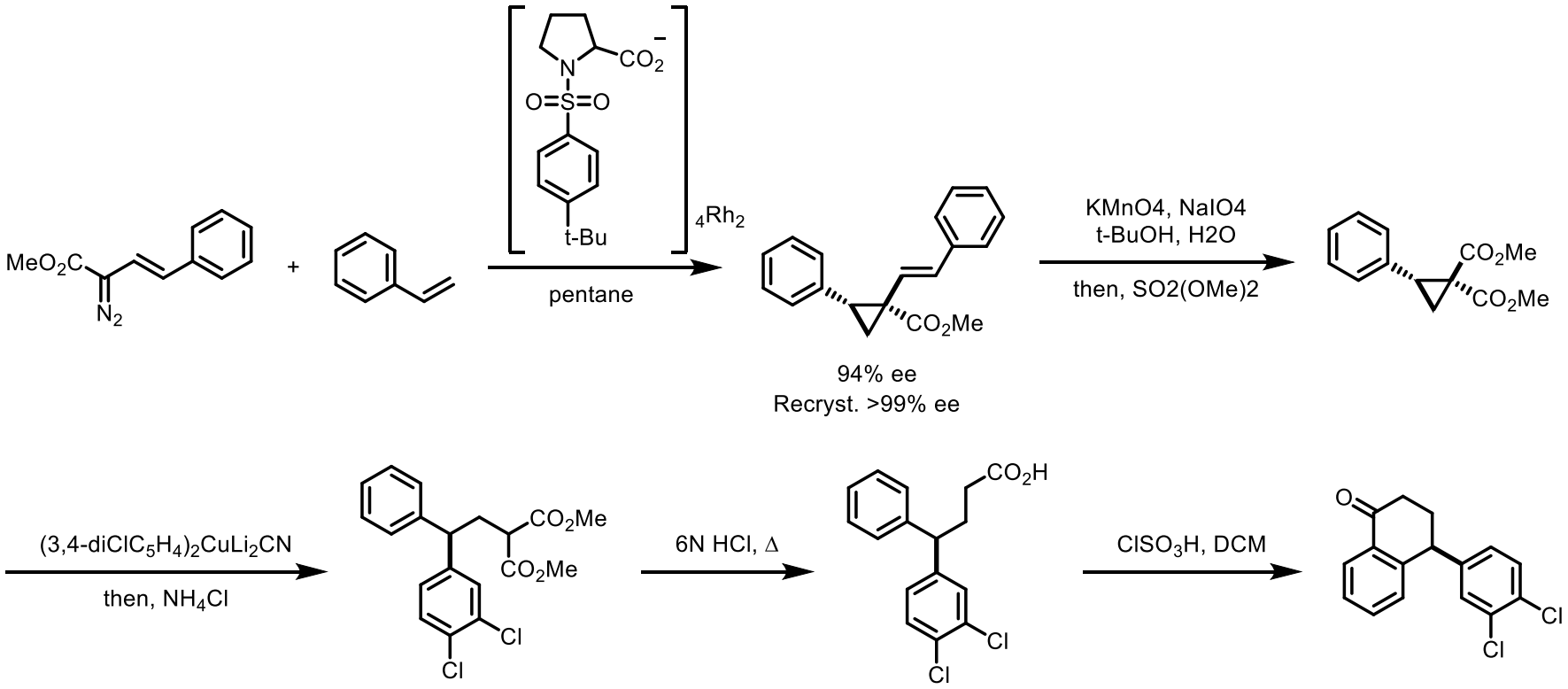


serotonin

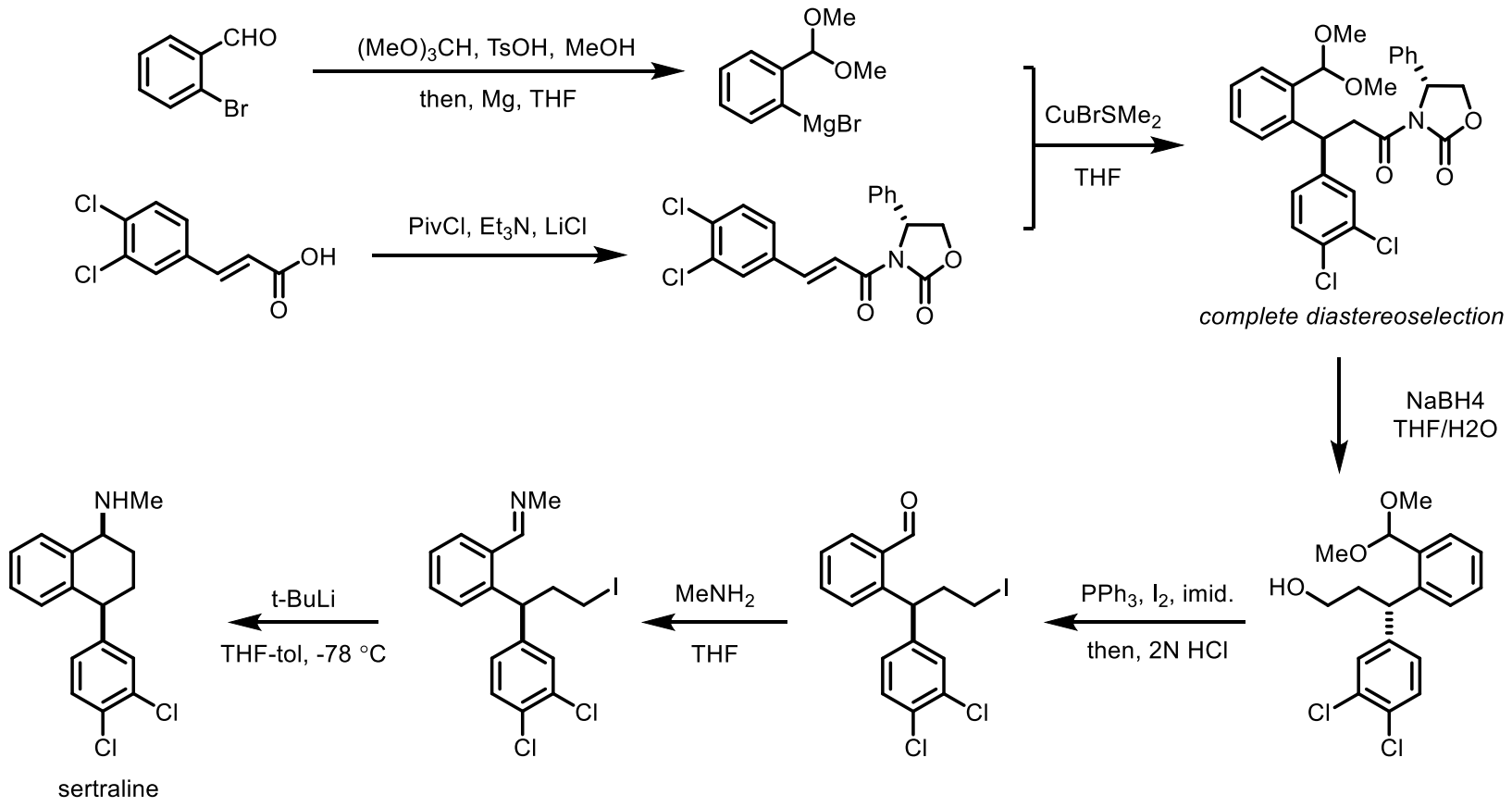
Early route to Sertraline (Zoloft) - Pfizer *Patent: US 4536518 (1985)*



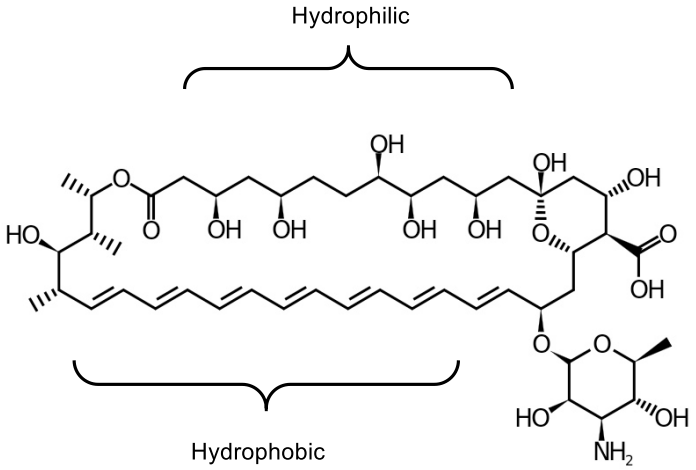
Enantioselective Route to Sertraline: Corey, TL, 1994, 5373



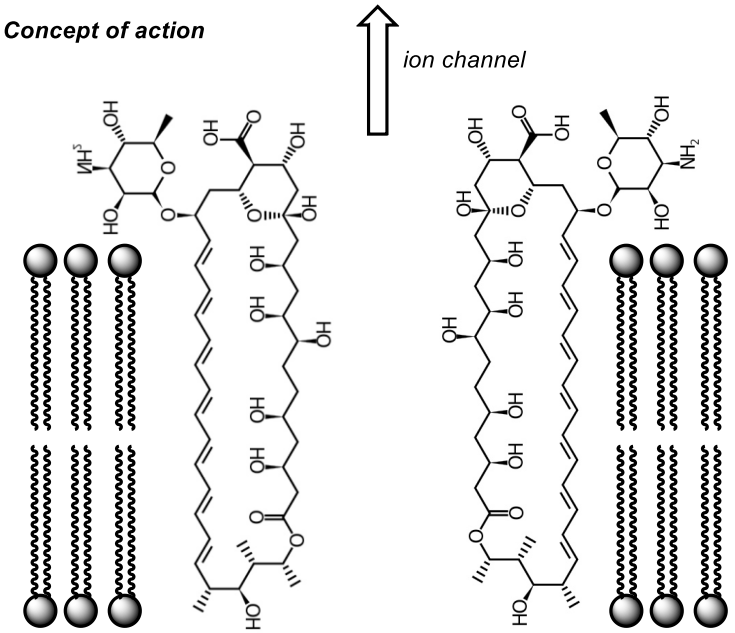
Merck Process: OL, 1999, 293

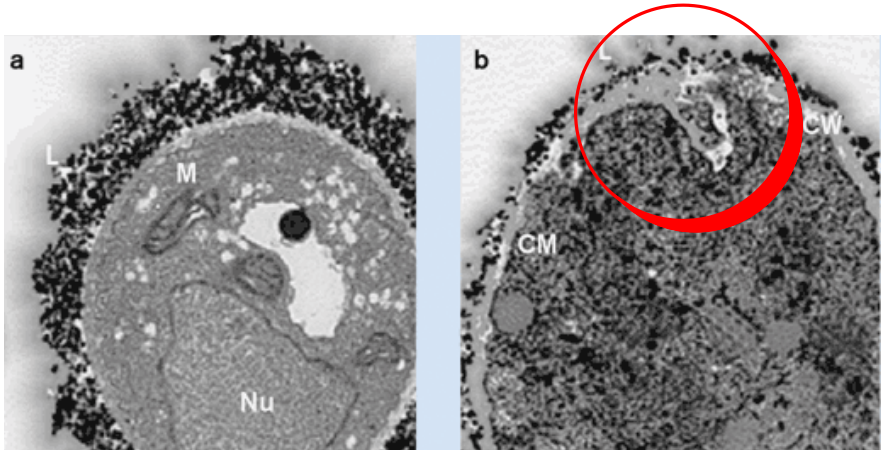


Amphotericin B - an anti-fungal agent



Concept of action





Bone Marrow Transplantation. AmBisome targeting to fungal infections. 1994;14:S3-S7

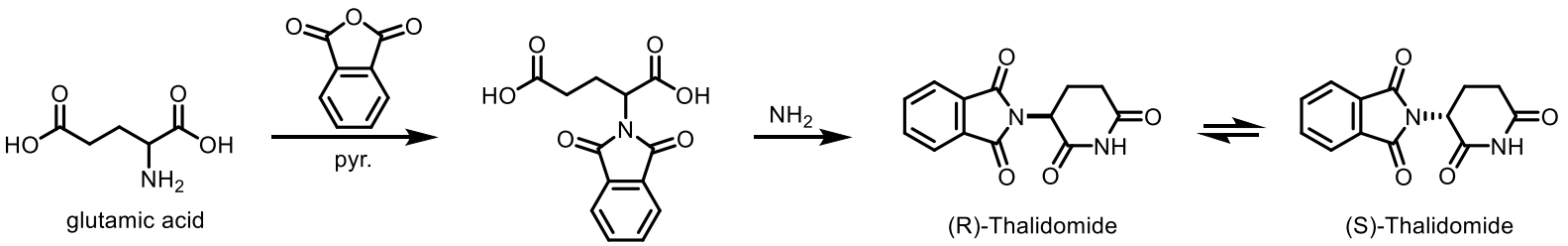
fumigatus incubated for 14 hours with gold-labeled liposomes:
(a) without AmBisome, showing lipid from the liposomes in association with the surface of the fungal cell wall.
(b) with AmBisome penetrating through the cell wall, and lipid accumulating in the cytoplasm.

Thalidomide Tragedy

"A compelling example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide to pregnant women in the 1960s. (*R*)-Thalidomide has desirable sedative properties, while its *S* enantiomer is teratogenic and induces fetal malformations. Such problems arising from inappropriate molecular recognition should be avoided at all costs."

Ryoji Noyori – Nobel Lecture 2001

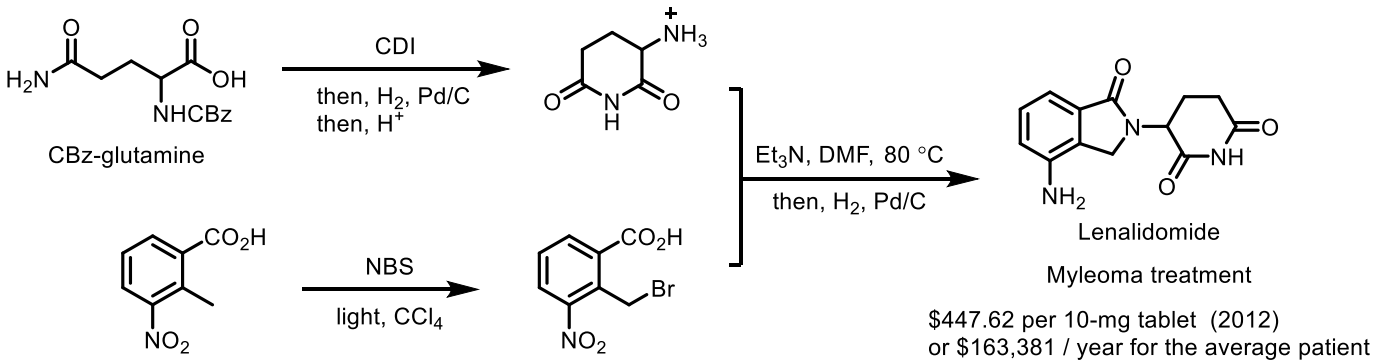
Thalidomide route



rapid interconversion in vivo

Thalidomide also found to be effective for treatment of certain cancers

Celgene. Med Chem. Bioorg. Med. Chem. Lett. 1999 1625



Myeloma treatment

$447.62 per 10-mg tablet (2012)
or $163,381 / year for the average patient

Thank you for your attention!

Main Sources:

The Organic Chemistry of Drug Synthesis Vol I-V (Daniel Lednicer)
Strategies for Organic Drug Synthesis and Design (Daniel Lednicer)
An Introduction to Medicinal Chemistry (Graham Patrick)
Top Drugs, Top Synthetic Routes (John Saunders)
Molecules and Medicine (Corey, Czako, Kurti)
Contemporary Drug Synthesis (Jie Jack Li)