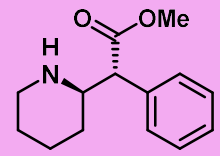
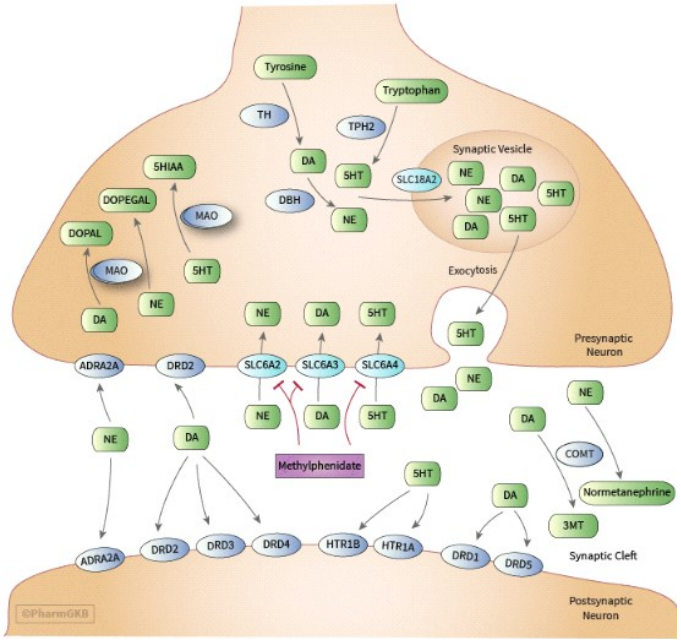
DOTW: Methylphenidate (Ritalin®)



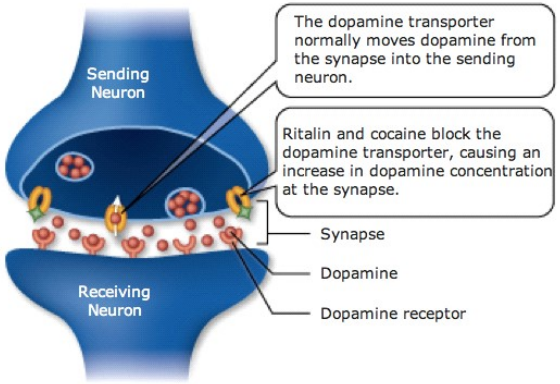
***d-threo*-methylphenidate**

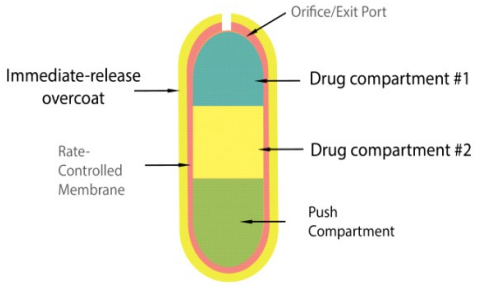
- first synthesized in 1944 by Leandro Panizzon at Novartis
  - named drug after his wife Rita who used it for low blood pressure
- identified as CNS stimulant in 1954
  - used first to treat barbiturate-induced coma, narcolsepy, depression, and memory deficits in elderly; eventually used to treat ADHD (starting 1960s)

NOVARTIS

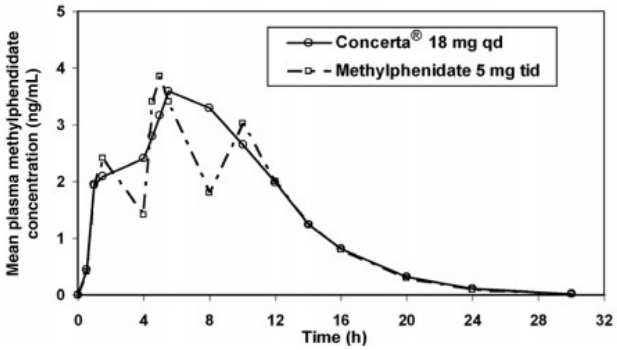


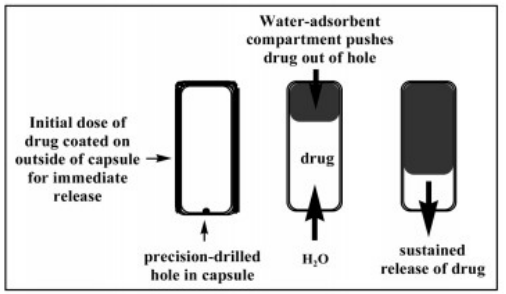
- metabolism: ester hydrolyzed to phenyl-piperidine acetic acid (PPA), which has little or no pharmacologic activity
- rapid and essentially complete absorption
  - peak absorption after about 2 hours
- acts as a norepinephrine and dopamine reuptake inhibitor (NDRI)
  - similar to cocaine but does not promote dopamine release from synaptic vesicles
- dose-related effect:
  - higher doses: increase norepinephrine and dopamine efflux throughout brain, leading to impaired cognitions and increased movement and impulsivity
  - lower doses: selectively activate norepinephrine and dopamine neurotransmission within prefrontal cortex
    - thus alleviating impulsivity and hyperactivity, increasing attention span and working memory





- Concerta utilizes osmotic pressure to deliver methylphenidate salt giving a sustained effect for 10-12 hours
- 22% of dose as an overcoat for immediate release (within an hour)
- 78% of dose gradually released
  - water permeates into core and causes the osmotically-active polymer to expand and slowly excrete drug through laser-drilled hole over 6-7 hours



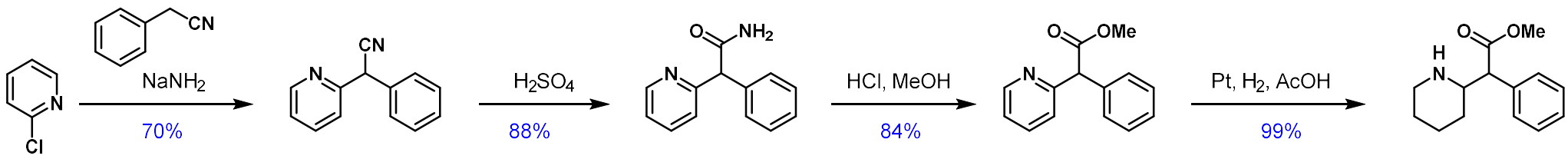


Overview of the OROS technology used in Concerta®

Clin Pharmacokinet., **1999**, *37*, 457. Gray, D. L. in *The Art of Drug Synthesis*, **2006**, 241. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021121s014lbl.pdf

DOTW: Methylphenidate (Ritalin®)

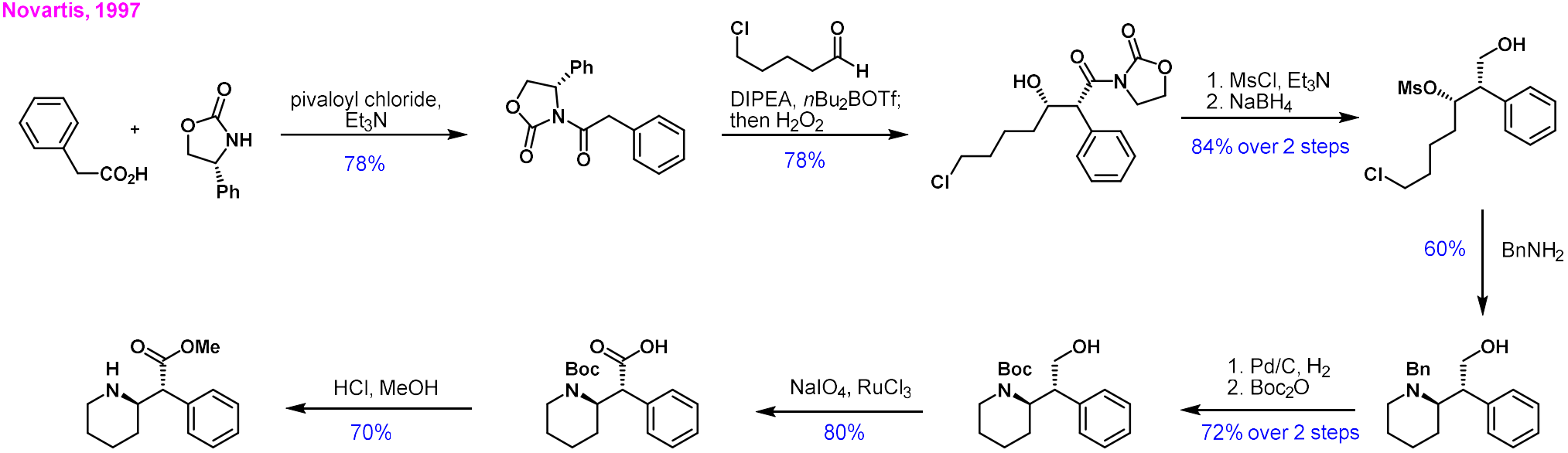
Discovery Route: Novartis, 1944



Asymmetric Routes:

J. Org. Chem., **1998**, *63*, 9628.

Novartis, 1997



Winkler, 1998