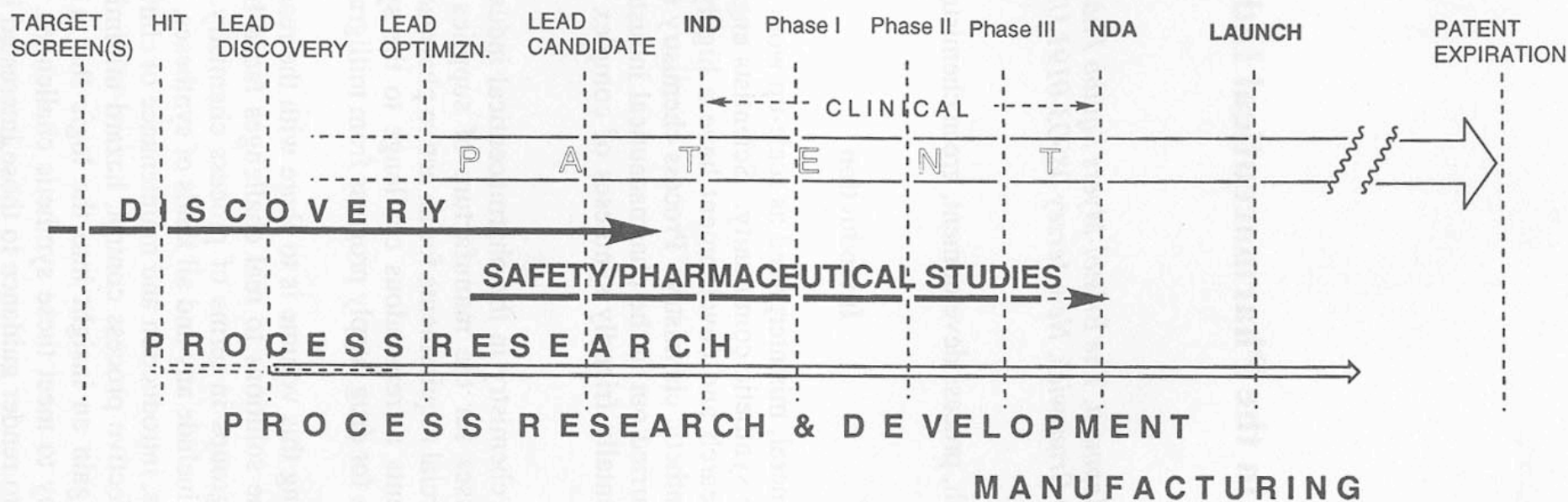


# From Benchtop to Process Plant in the Pharmaceutical Industry

Danielle Jacobs  
Crimmins' Group Meeting  
9/28/05

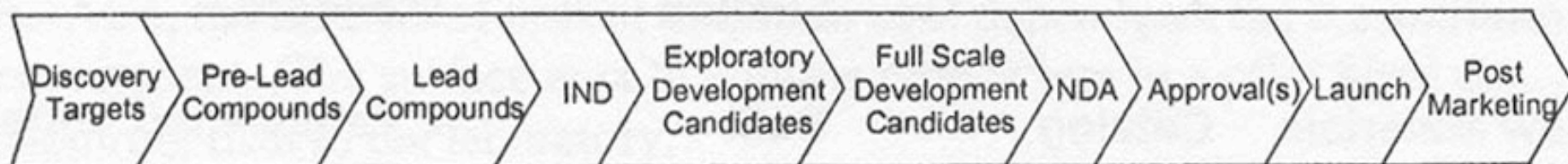
# PHARMACEUTICAL DRUG DEVELOPMENT EVENTS

## A SIMPLIFIED VIEW



- Increasingly complex molecules
- Stricter purity specifications
- Government regulations

# The Drug Discovery & Development Process Map



200-400 grams

2-4 Kg: Toxicology / Preformulation

20-40 Kg: Toxicology / Phase I Supplies

40-50 Kg: Formulation Development / Phase II

50-200 Kg: Formulation Pilot / Phase III

100-1000 Kg: Demonstration / Validation

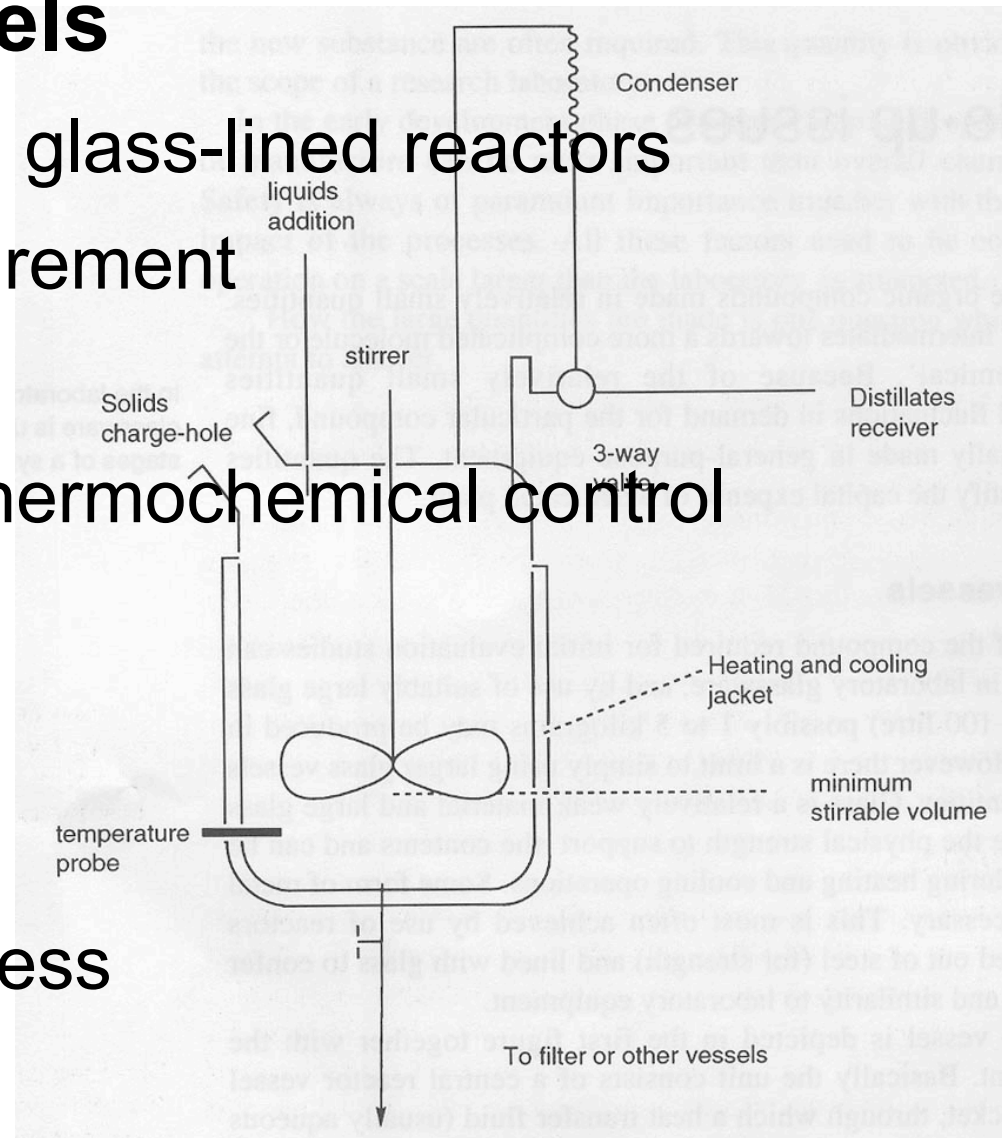
1000-10,000 Kg: Launch Supplies

# Scale-Up Issues



# • Reaction Vessels

- Steel-encased, glass-lined reactors
- Volume measurement
- Temperature/thermochemical control
- Reaction time
- Reaction progress
- Extraction



- **Isolation of Products**

- Crystallization
- Pressure filtration/drying of solids
- Telescoping
- Solvent distillation
- Chromatography avoided
  - Large solvent volume
  - Decreased efficiency

- **Choice of Synthetic Route**
  - Starting materials
    - Availability, cost efficient
    - Number of steps, yield
    - Atom efficiency
  - Environmental/health safety
    - Material transportation
    - Waste minimization
    - Practices follow FDA/EPA guidelines of pollution control

- Solvent
  - Readily recovered/recyclable
  - Non-toxic, environmentally friendly
  - ex; H<sub>2</sub>O, PhCH<sub>3</sub>, MTBE, EtOAc, hexanes

Solvent	Concentration Limit	Concern	Typical Replacement
benzene	2 ppm	carcinogen	toluene
carbon tetrachloride	4 ppm	toxic & environmental hazard	ethyl acetate
1,2-dichloroethane	5 ppm	toxic	ethyl acetate
1,1-dichloroethane	8 ppm	toxic	ethyl acetate
1,1,1-trichloroethane	1500 ppm	environmental hazard	ethyl acetate

<b>Solvent</b>	<b>Concentration Limit (ppm)</b>
acetonitrile	410
chlorobenzene	360
chloroform	60
dichloromethane	600
1,2-dimethoxyethane	100
N,N-dimethylformamide	880
1,4-dioxane	380
2-ethoxyethanol	160
ethyleneglycol	620
formamide	220
hexane	290
2-methoxyethanol	50
methylbutyl ketone	50
nitromethane	50
pyridine	200
sulfonane	160
tetralin	100
toluene	890
1,1,2-trichloroethene	80

acetic acid	ethanol	methylisobutyl ketone
acetone	ethyl acetate	2-methyl-1-propanol
anisole	ethyl formate	pentane
1-butanol	formic acid	1-pentanol
2-butanol	heptane	1-propanol
butyl acetate	isobutyl acetate	propyl acetate
<i>t</i> -butyl methyl ether	methyl acetate	tetrahydrofuran
cumene	3-methyl-1-butanol	
dimethyl sulfoxide	methylethyl ketone	

- Reagents
  - Non-toxic, environmentally friendly
  - Oxidants
    - Peroxides preferred over metal oxidants and ozone
  - Reducing Agents
    - H<sub>2</sub> on metal catalyst preferred over LAH
    - NaBH<sub>4</sub>, DIBAL, metal reductants
  - Enzyme catalysis

- Acids and Bases
  - $\text{H}_2\text{SO}_4$  preferred over  $\text{HCl}$  and  $\text{H}_3\text{PO}_4$
  - $p\text{TsOH}$  and  $\text{CH}_3\text{SO}_3\text{H}$  help form crystalline salts
  - $(\pm)\alpha$ -Methylbenzylamine helps form diastereomeric salts
  - $n\text{BuLi}$  discouraged due to pyrophoric nature

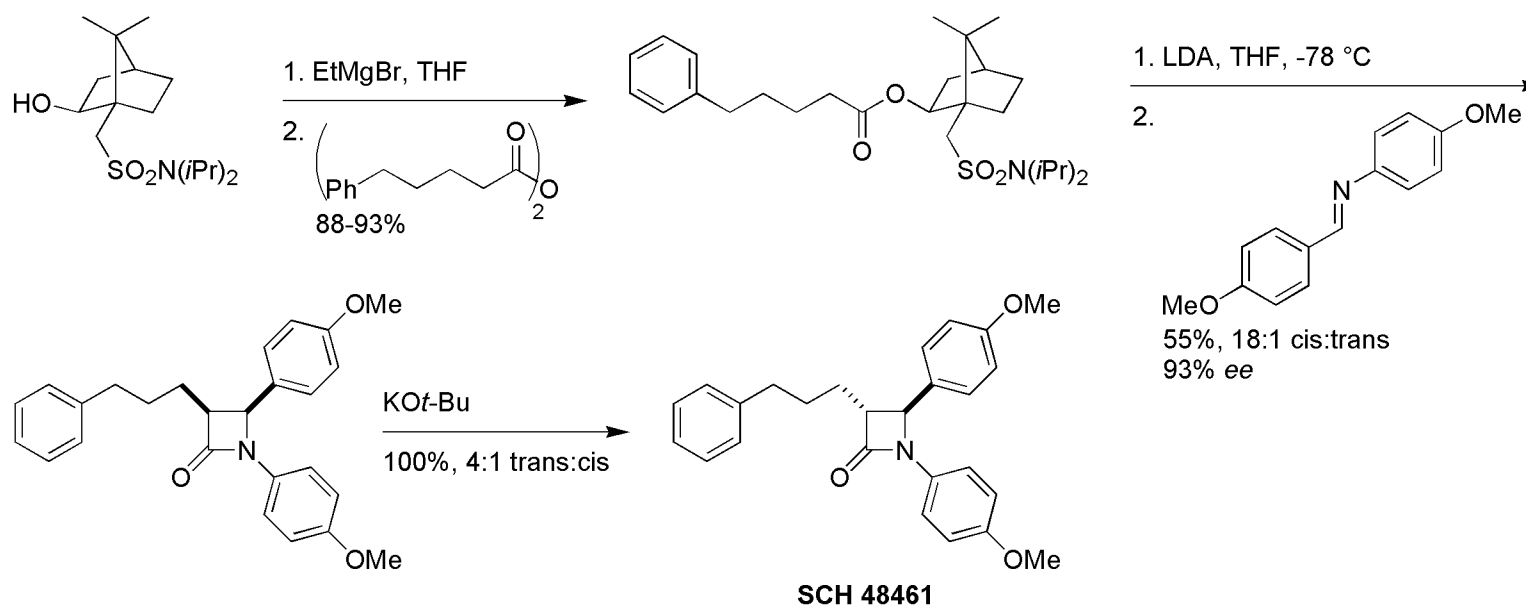
<b>LD<sub>50</sub> (mg/Kg)</b>	<b>Toxicity</b>
< 0.5	dangerously toxic
0.5 – 50	seriously toxic
50 – 500	very toxic
500 – 2,000	moderately toxic
2,000 – 15,000	slightly toxic
> 15,000	low toxicity

# Synthetic Routes

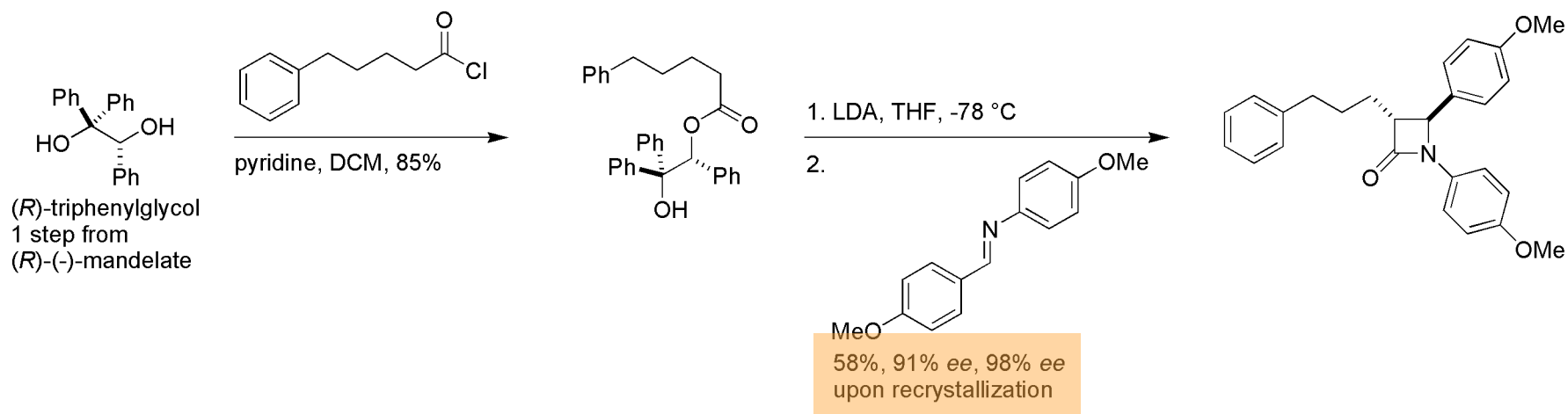
- Discovery
  - Grams
  - Route allows for expedient synthesis of several analogs for biological evaluation
  - Racemic synthesis
- Pilot
  - Kilograms (clinical trials)
  - Optimization of large-scale enantiospecific synthetic route
- Manufacturing
  - Tons

# SCH 48461: Discovery

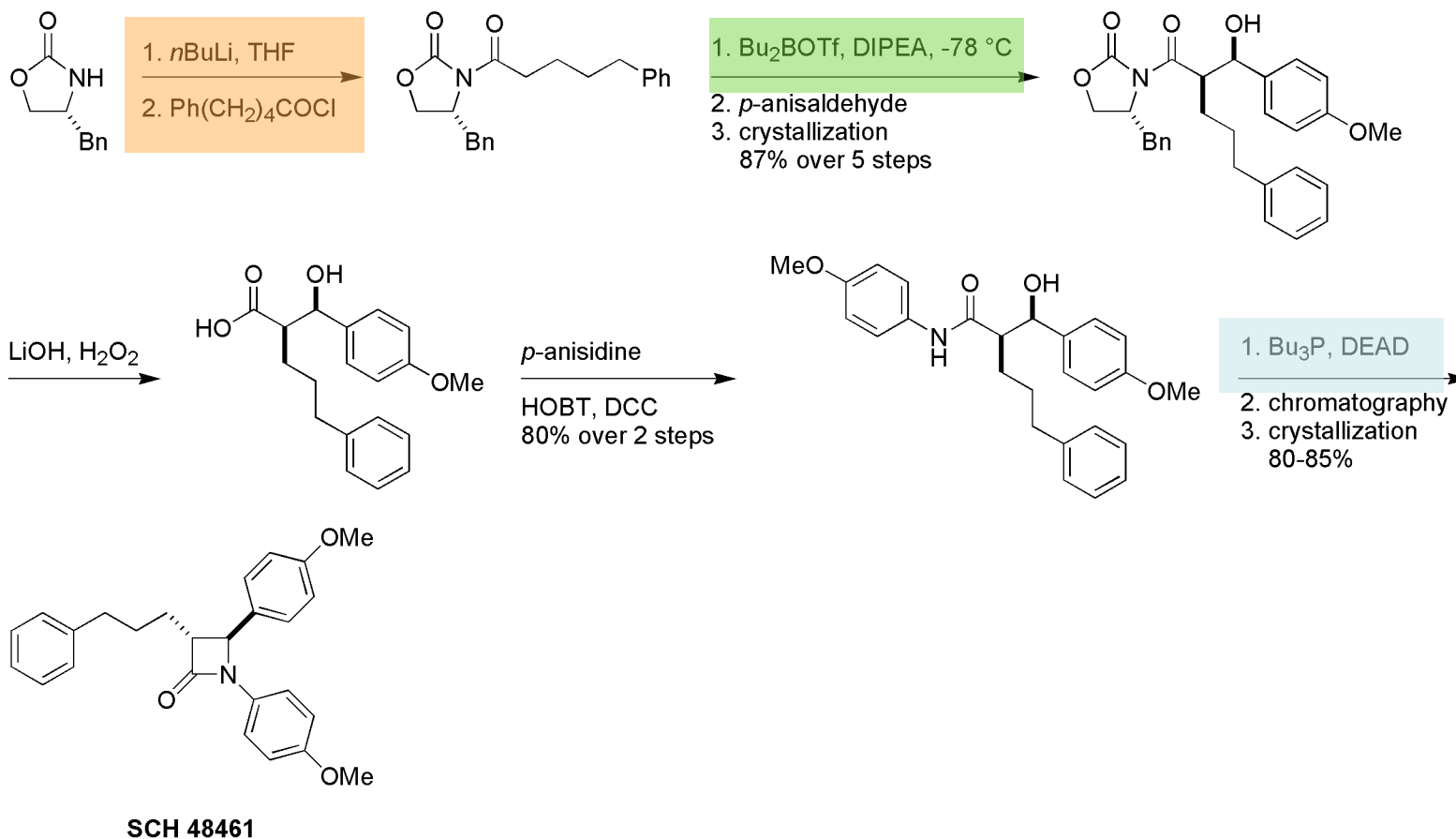
- Discovered by Schering-Plough in 1994 while investigating various azetidinones as potent cholesterol absorption inhibitors



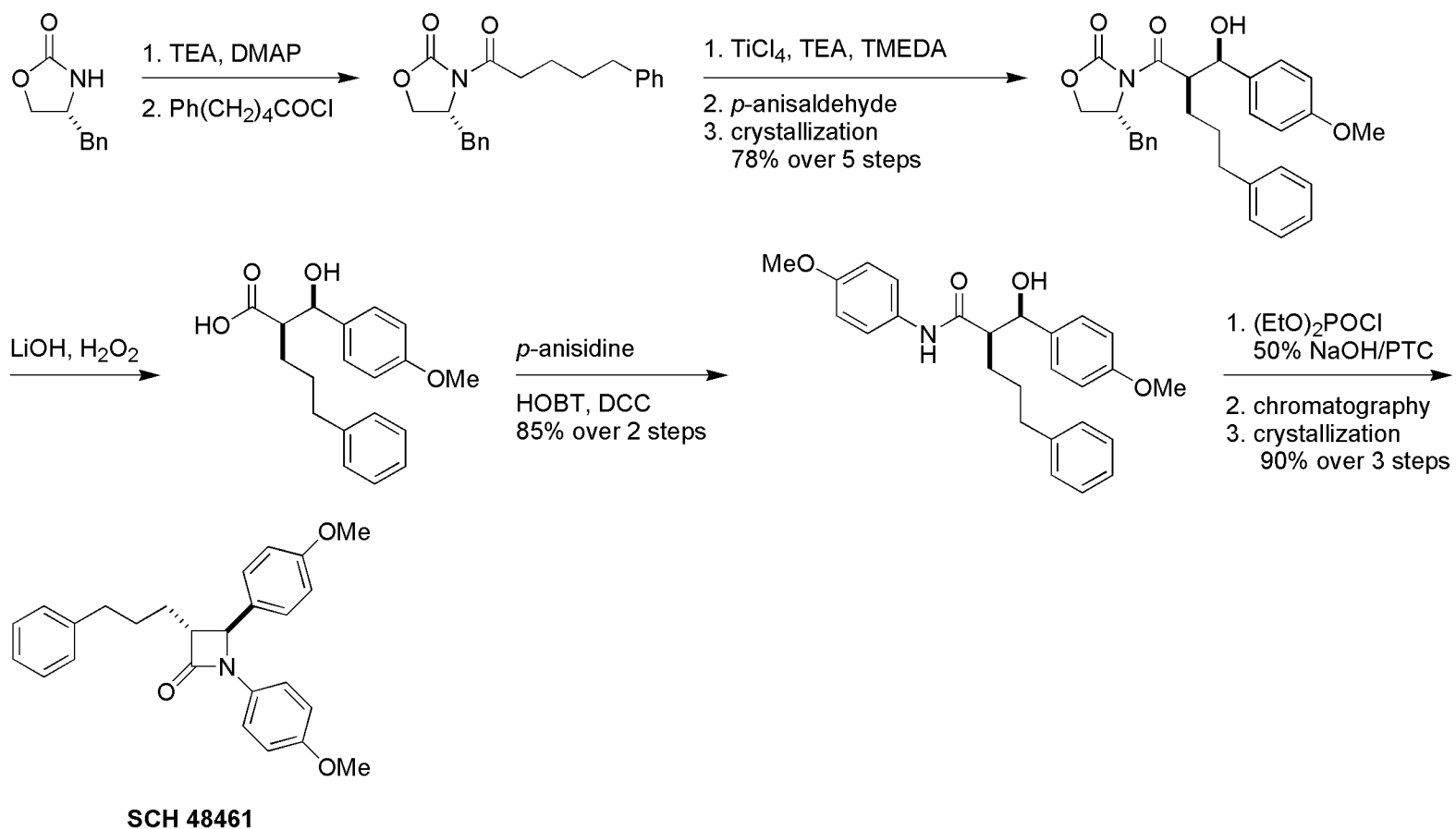
- Difficult crystallization makes purging of diastereomers via crystallization problematic
- No useful functional group for chemical resolution
- Epimerization and prep-scale HPLC not practical for clinical trials that require >98% ee
- Low yields of imine coupling/cyclization



# SCH 48461: Pilot Scale-Up

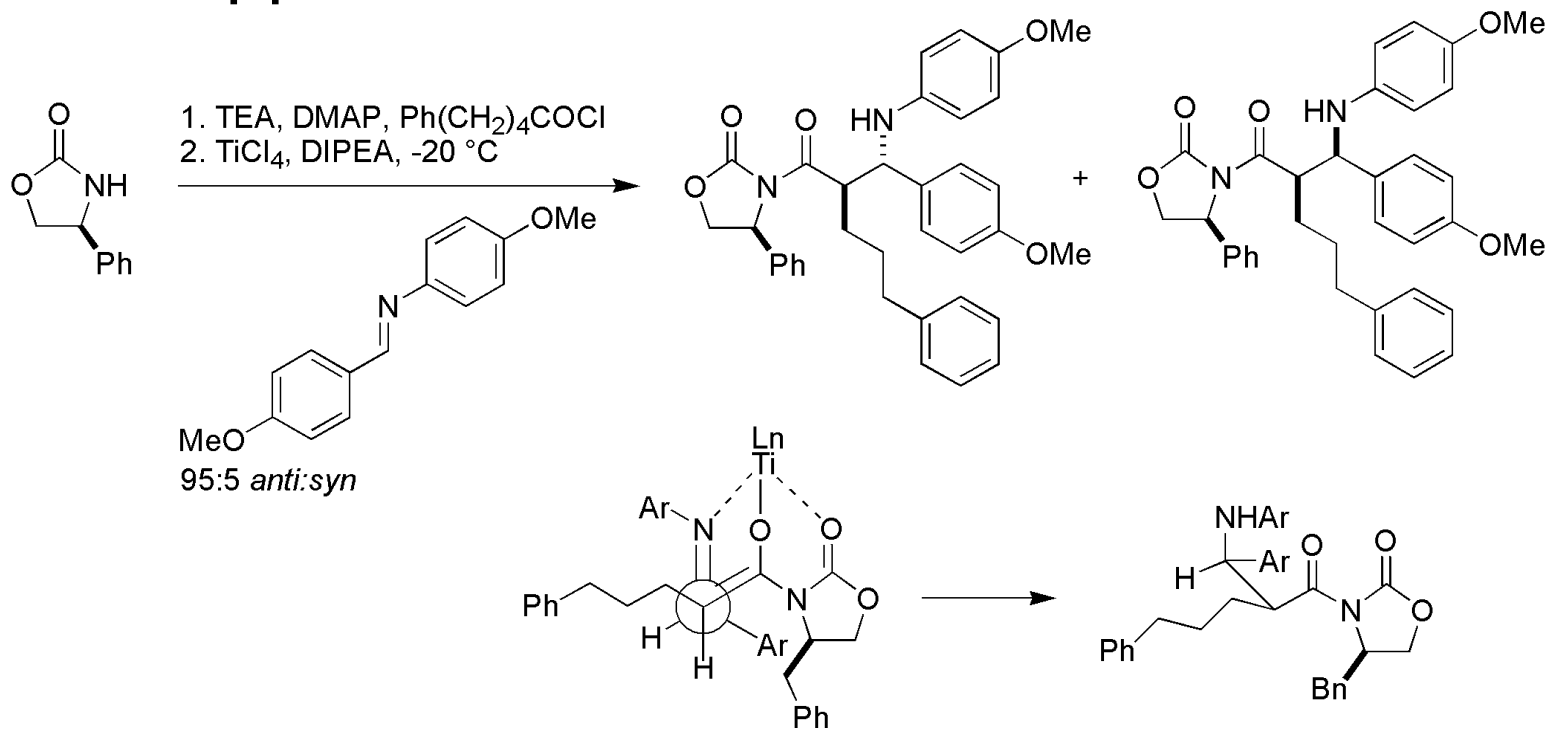


# SCH 48461: Pilot Scale-Up



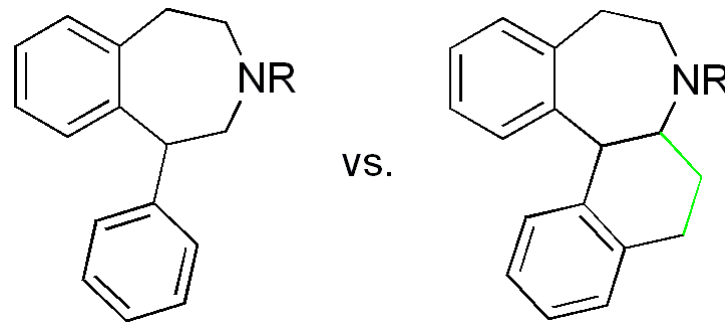
# SCH 48461: Imine Addition

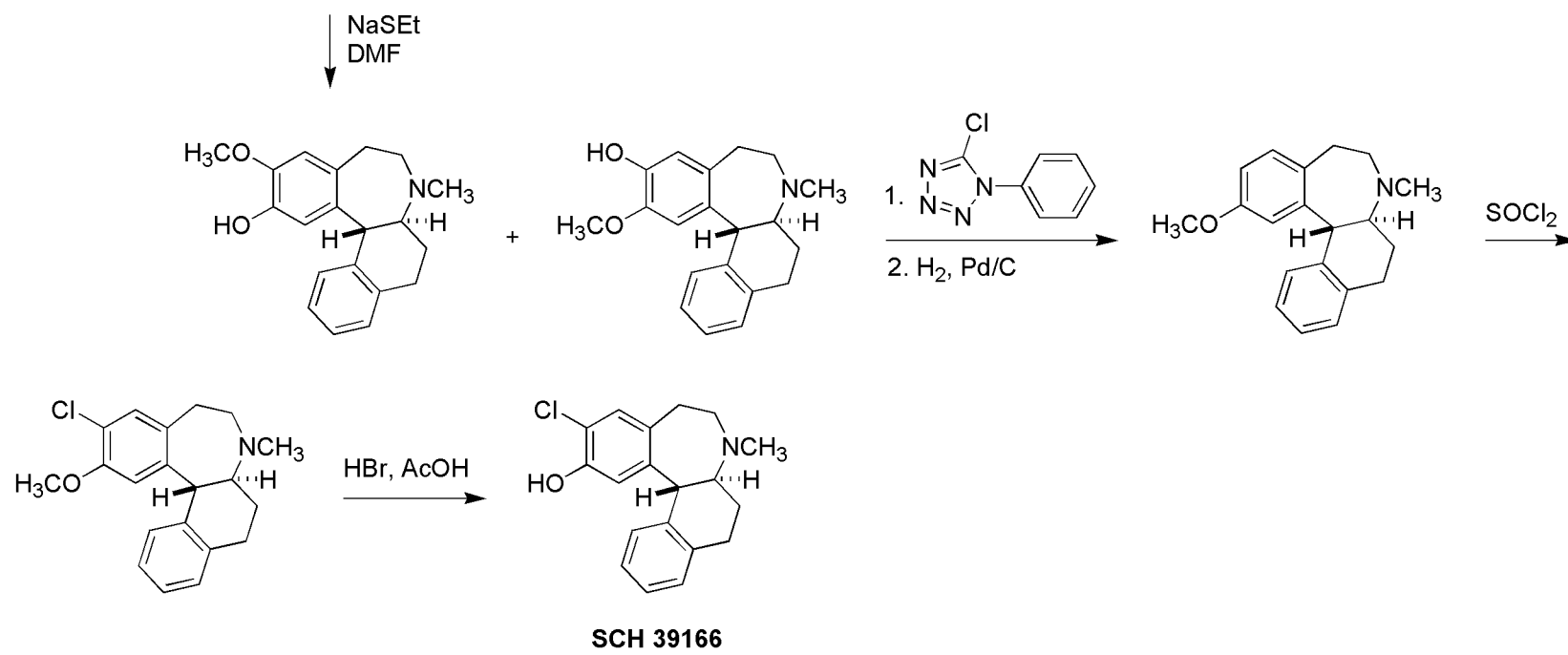
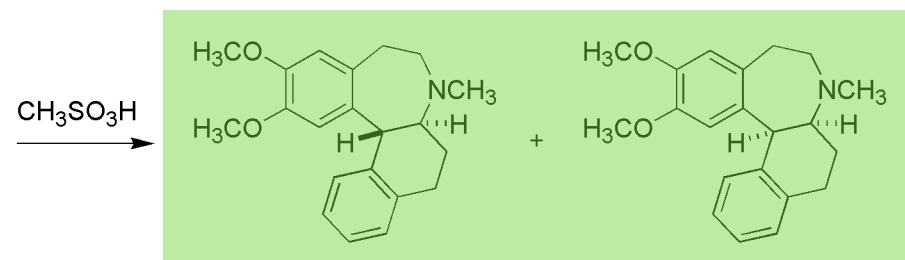
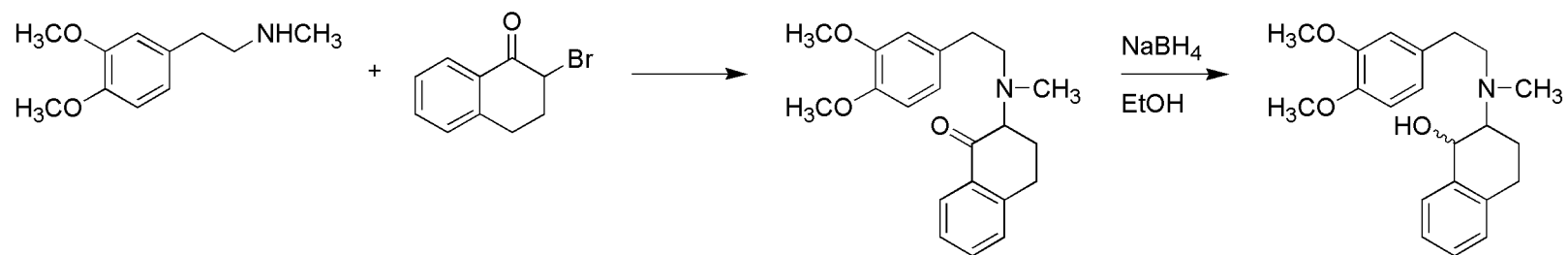
- Favored due to long synthetic sequence, chromatographic purification, and utilization of expensive chiral unnatural oxazolidinones of aldol approach



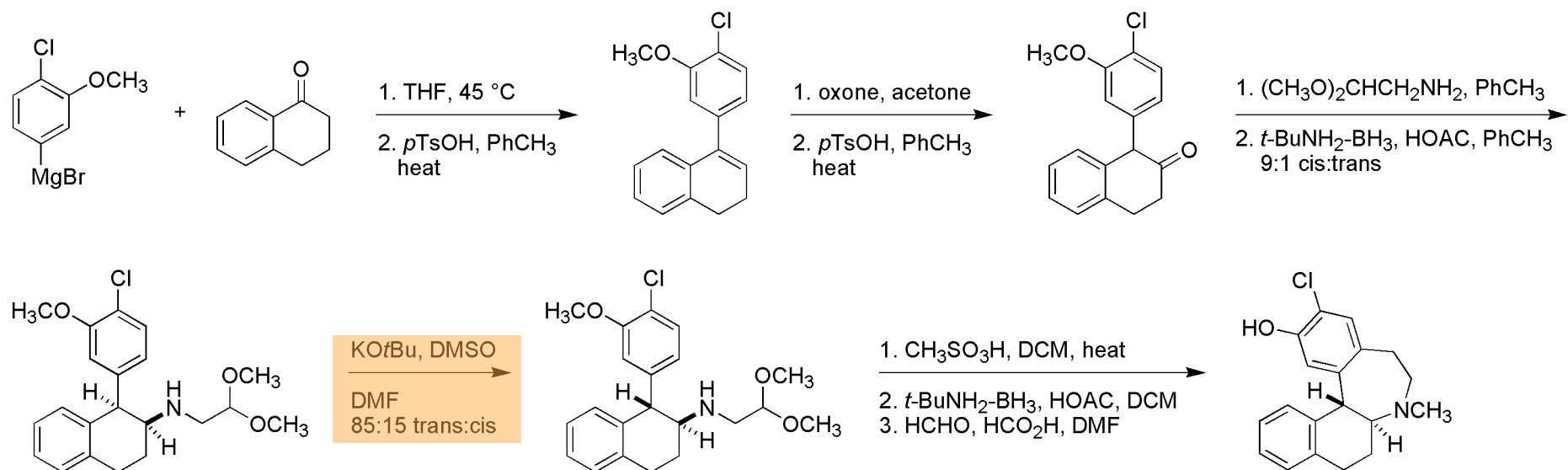
# SCH 39166: Discovery

- Benzazepines investigated in 1989 by Schering-Plough as selective dopamine D1 antagonists
- Developed later for treatment of schizophrenia and other D1-dependent neurological disorders
- Reactivity above other benzazepines thought to be due to ethylene bridge ( $ED_{50} = 0.01$  mg/kg)



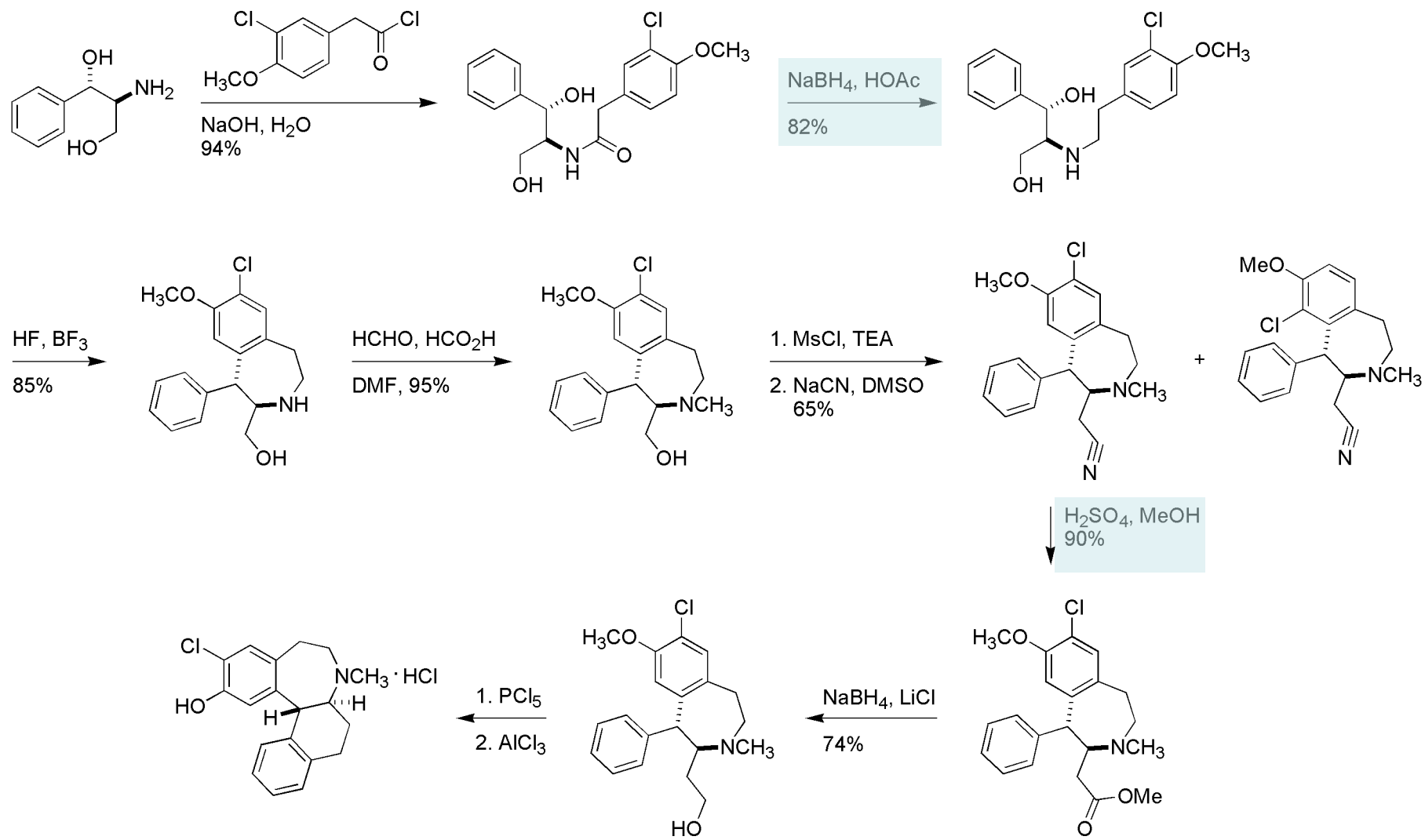


# SCH 39166: Pilot Scale-Up

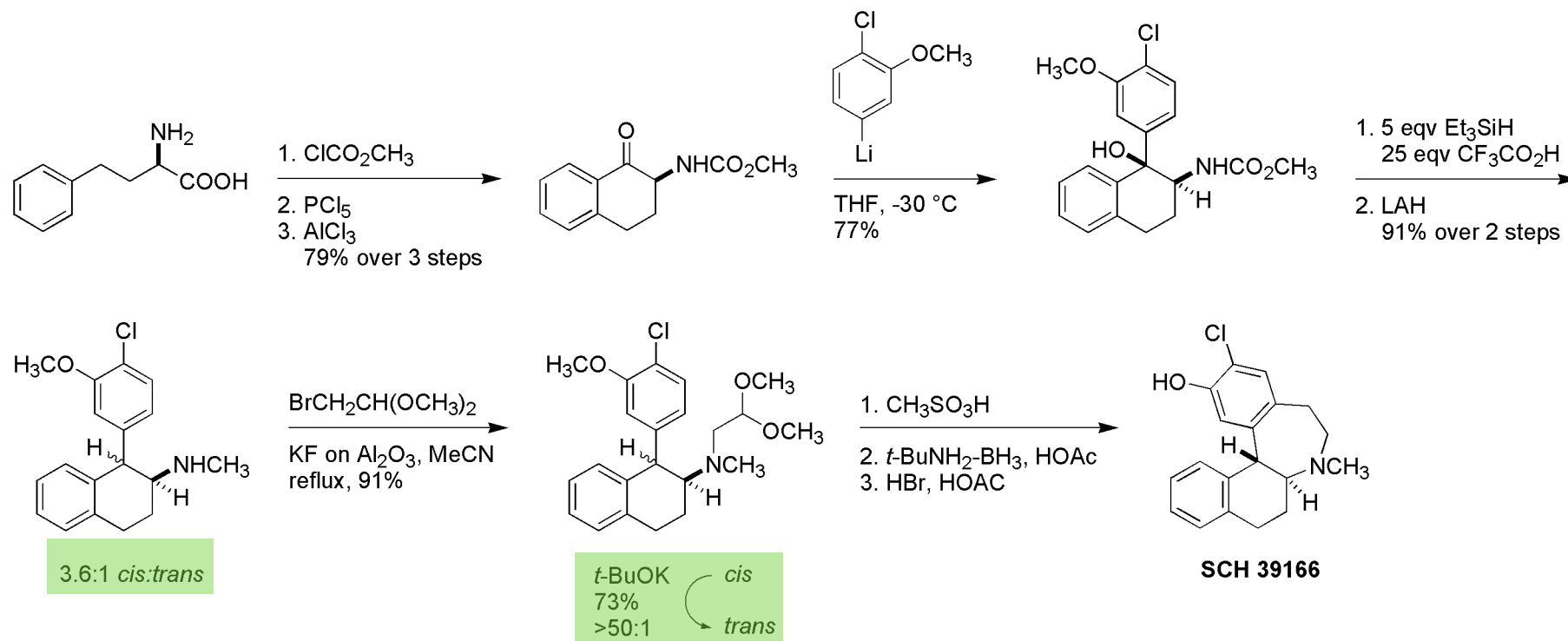


- Route still lacks complete enantioselectivity and relies on a late-stage resolution

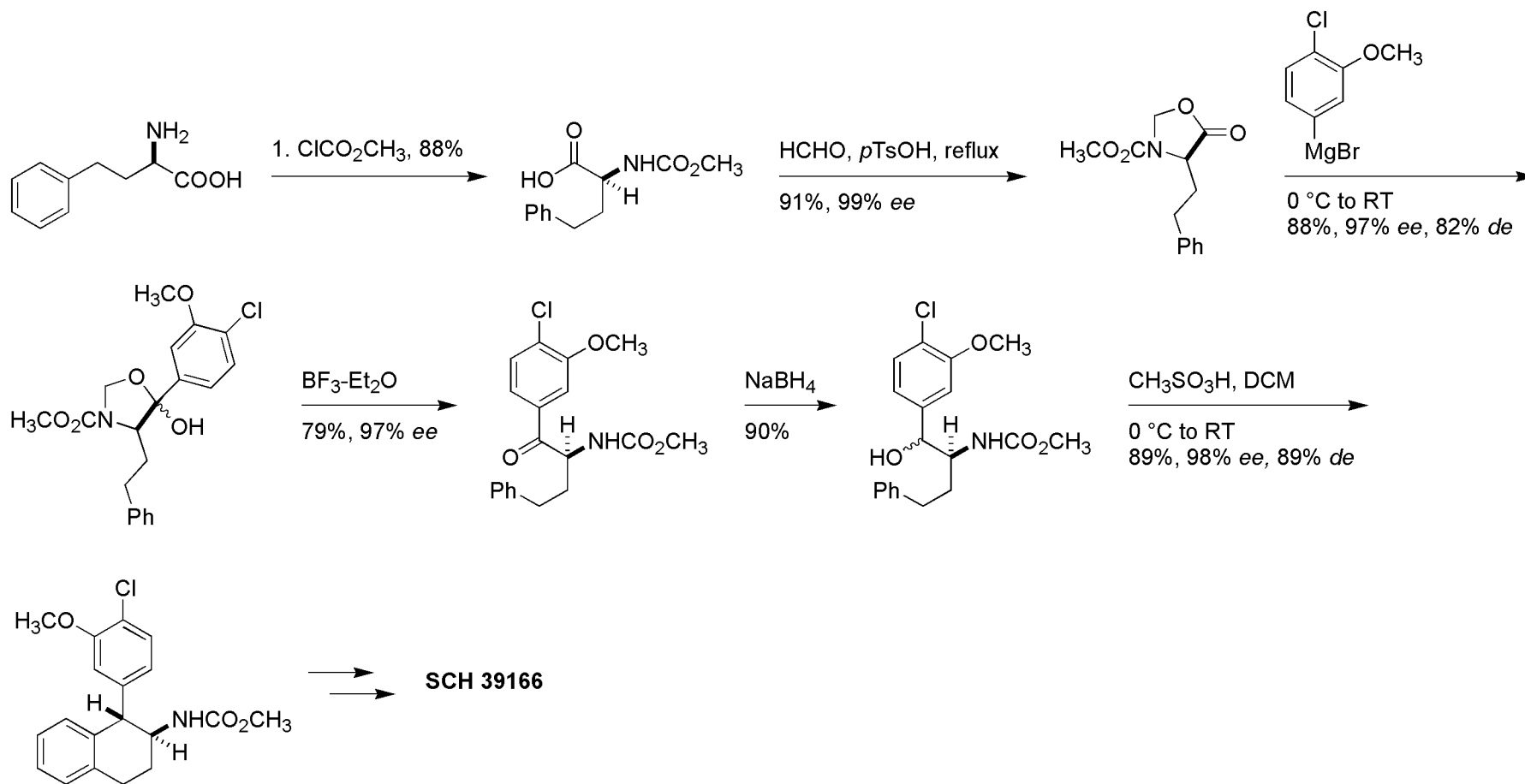
# SCH 39166: Enantioselective Approach



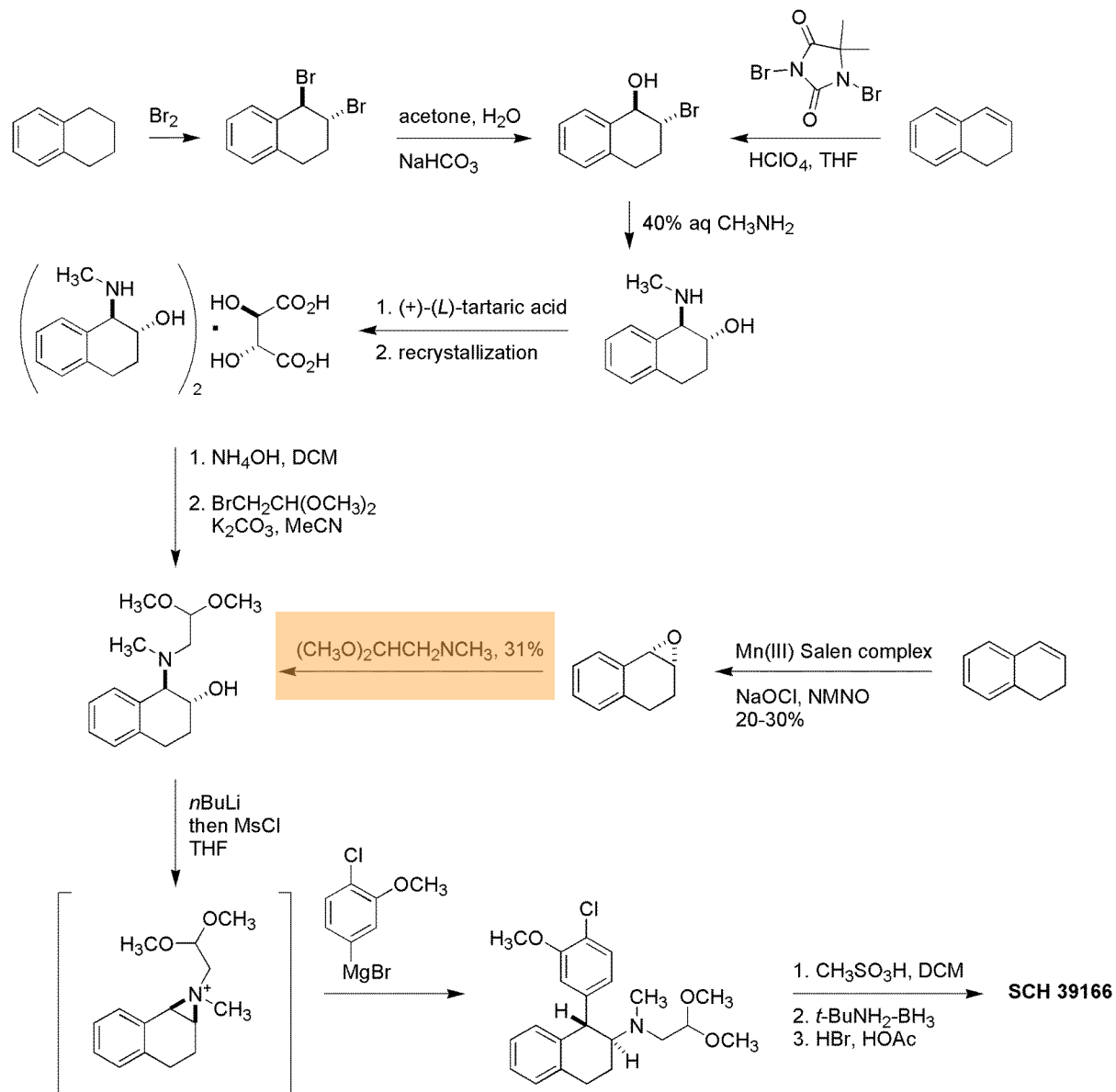
# SCH 39166: (+)-L-Homophenylalanine



# SCH 39166: (+)-L-Homophenylalanine

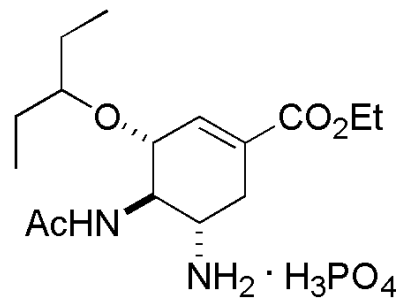


# SCH 39166: Aziridinium Salt Approach



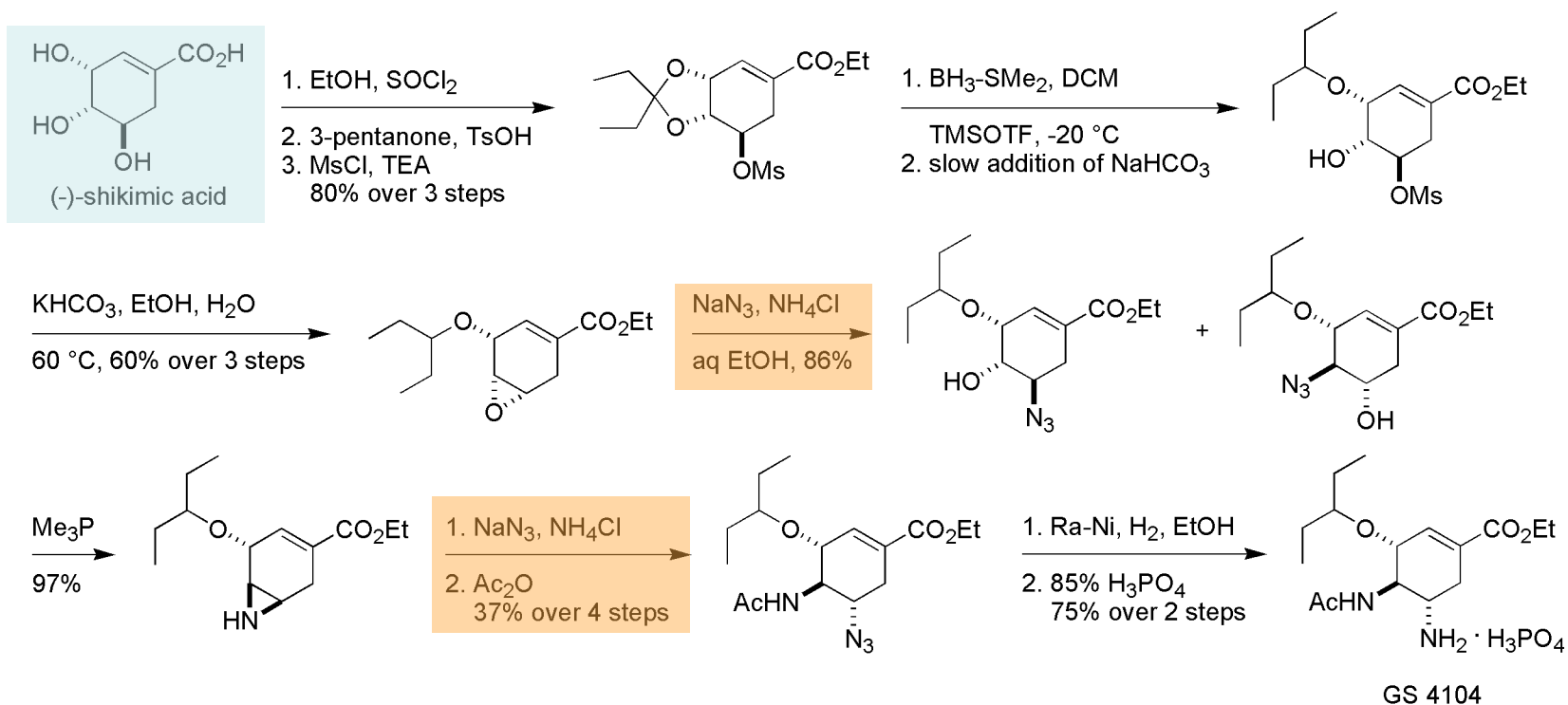
# GS 4104 Oseltamivir Phosphate

- Potent inhibitor of viral neuroaminidase
- Discovered and developed by Gilead Sciences as an orally active pro-drug for viral influenza
- Collaborations with Hoffmann-La Roche
- Drug marketed today as Tamiflu
- Increased yields from 29-38% to 61% overall on production scale



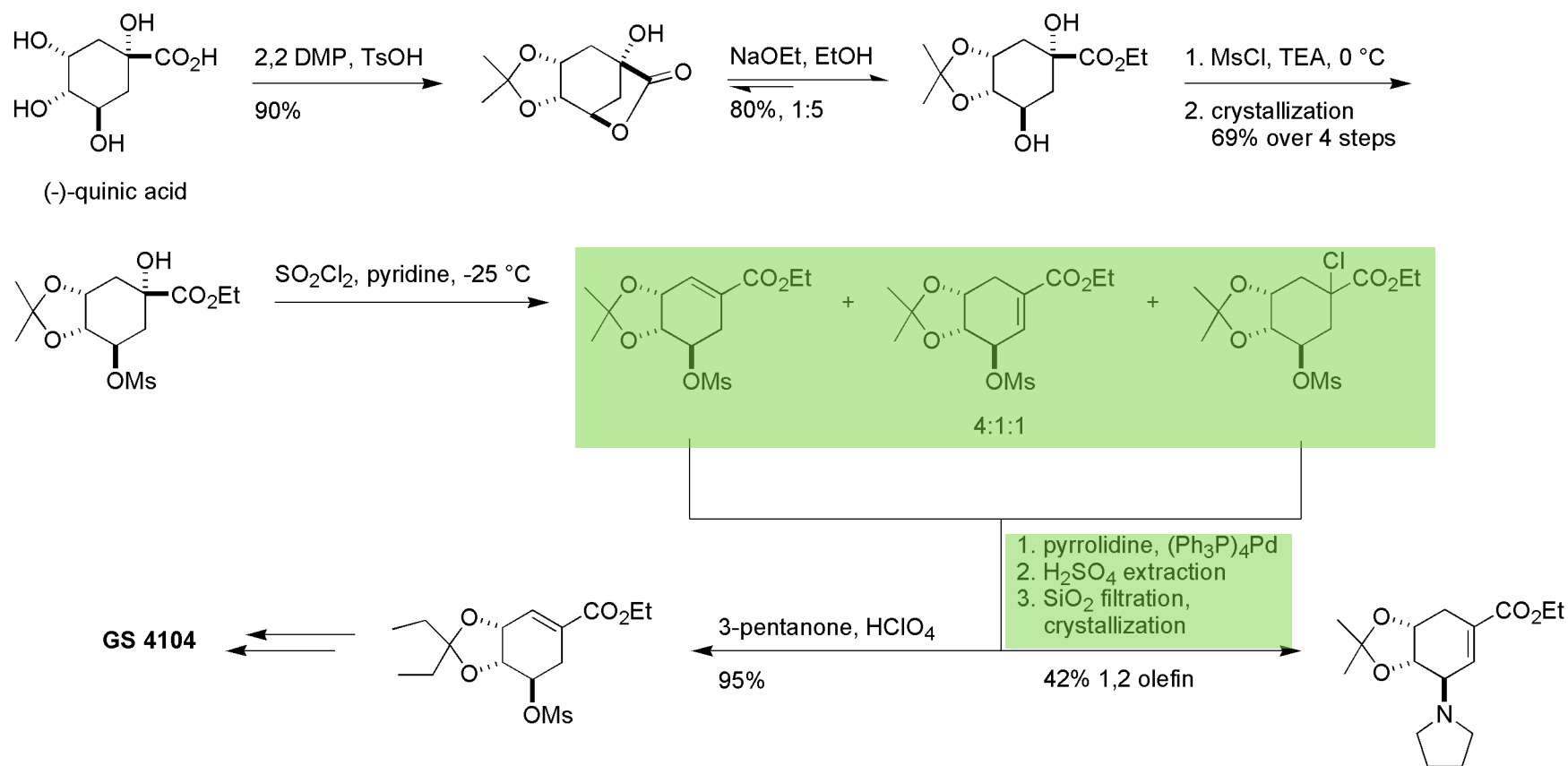
# GS 4104: Discovery Team Synthesis

- 10 steps, 21% yield from (-)-shikimic acid



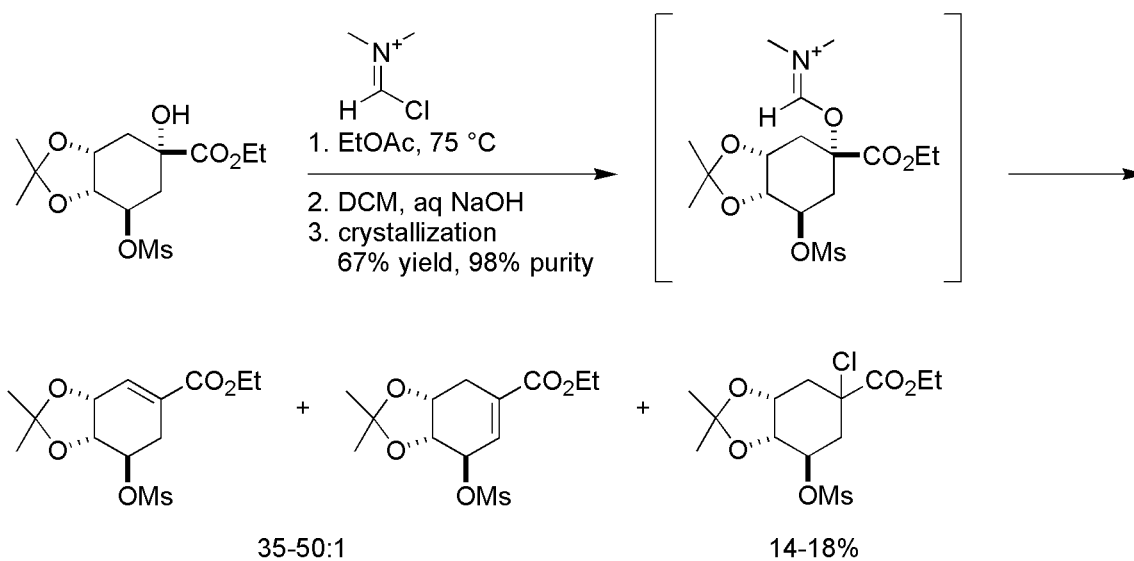
# GS 4104: Discovery Team Synthesis

- 12 steps, 4.4% overall yield from (-)-quinic acid



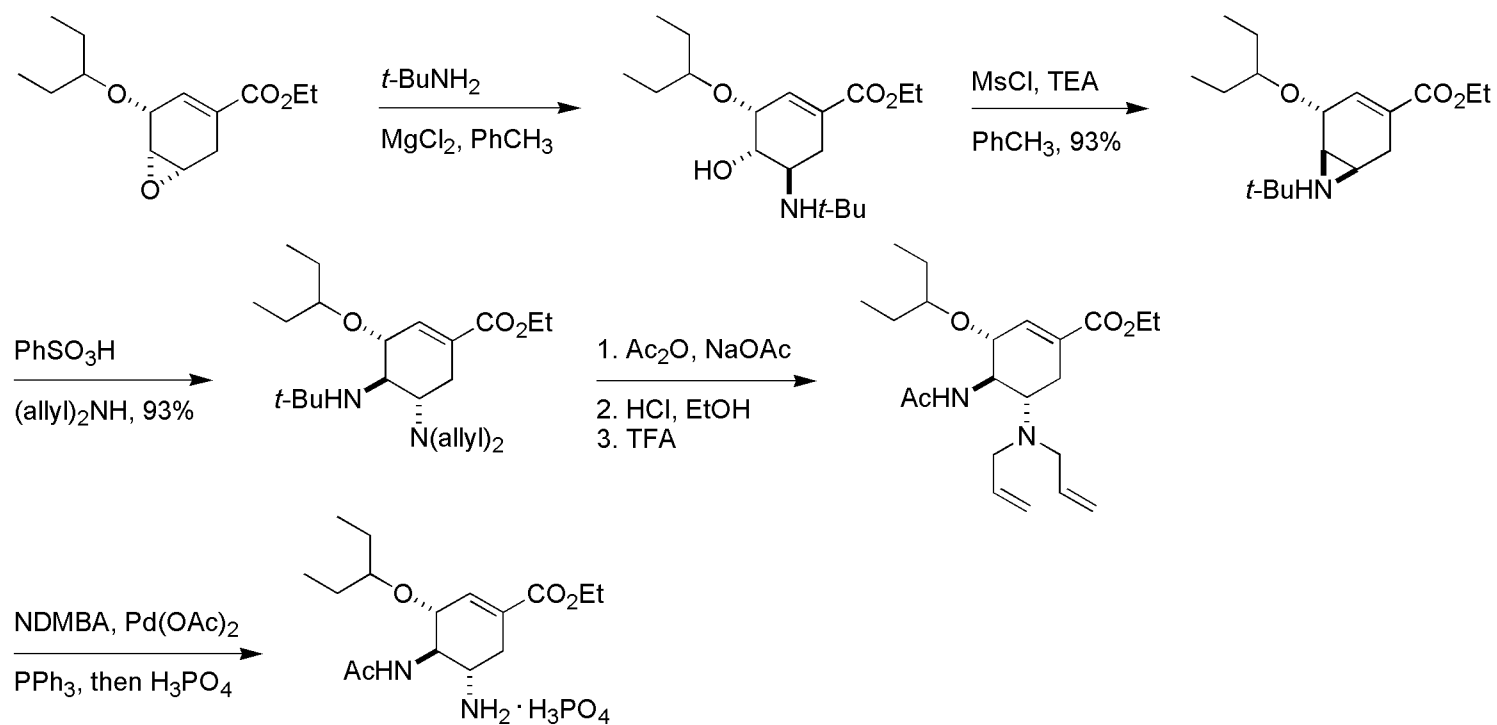
# GS 4104: Pilot Scale-Up

- Dehydration



# GS 4104: Pilot Scale-Up

- Azide Replacement



GS 4104

# Lead References

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