

CYCLIC AMINE PHARMACEUTICALS

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Shenvi Lab Group Meeting

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Prevalence

Table 4. Top 10 Reactions by Frequency in the 2008 Data Set

reaction	no. of reactions	% of all reactions
N-acylation to amide	1165	16.0
N-containing heterocycle formation	537	7.4
N-arylation with Ar-X	458	6.3
RCO ₂ H deprotection	395	5.4
N-subs with alkyl-X	390	5.3
reductive amination	386	5.3
N-Boc deprotection	357	4.9
Suzuki cross-coupling reaction	338	4.6
O-substitution	319	4.4
other NH deprotection	212	2.9
total	4557	62.4

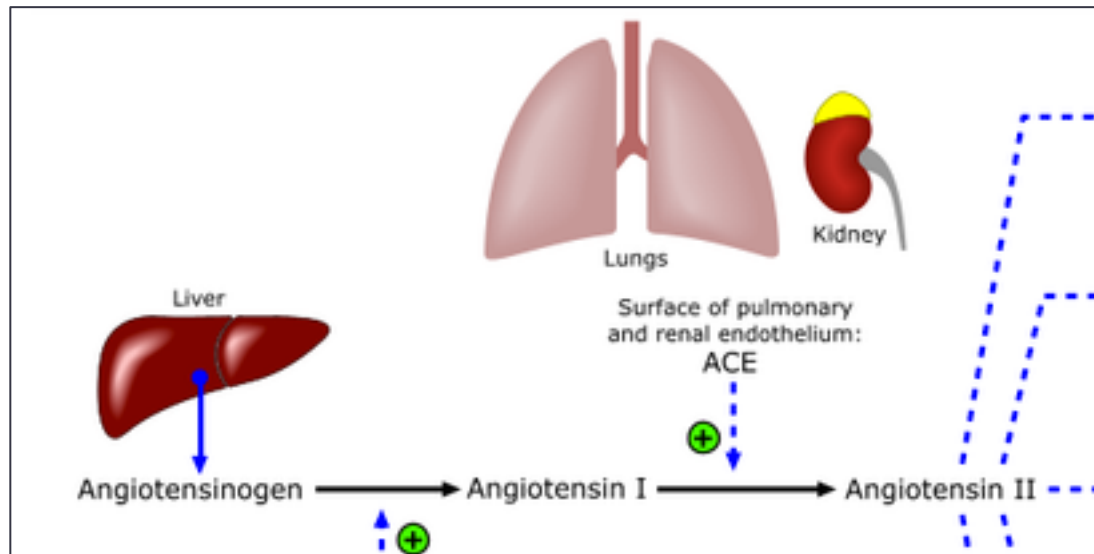
“With 42.9% of compounds containing an aliphatic amine, this group is one of the most popular functionalities outside the aromatic rings”

Amines in the Drug Market

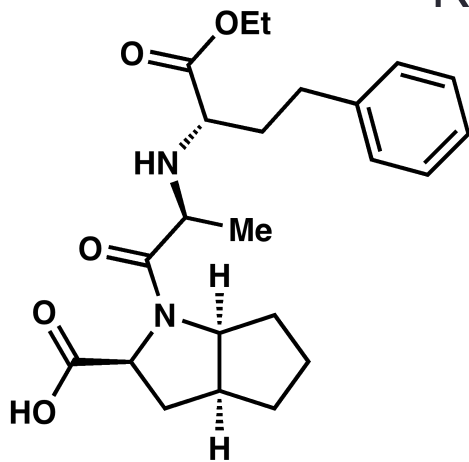
“Top 200 Brand-Name Drug by Retail Dollars in 2006”

<p>Company: 2006 Sales: Novartis \$1.30 Billion</p> <p>Profile: An antihistamine used to prevent and treat allergy symptoms.</p>	<p>2005 Rank: 31</p> <p>Company: 2006 Sales: Pfizer \$1.16 Billion</p> <p>Profile: An antihistamine used to prevent and treat allergy symptoms.</p>	<p>2005 Rank: 41</p> <p>Company: 2006 Sales: GSK \$1.16 Billion</p> <p>Profile: A beta blocker used to treat hypertension and heart failure.</p>	<p>2005 Rank: 36</p> <p>Company: 2006 Sales: GSK \$1.15 Billion</p> <p>Profile: An antiviral agent for treating shingles, cold sores, and genital herpes.</p>	<p>2005 Rank: 39</p> <p>Company: 2006 Sales: Merck \$1.15 Billion</p> <p>Profile: An antihyperlipidemic used to lower cholesterol levels.</p>
<p>Actonel</p> <p>Company: 2006 Sales: Amgen & G \$0.78 Billion</p> <p>Profile: Used to treat osteoporosis.</p>	<p>49 Omnicef</p> <p>2005 Rank: 58</p> <p>Company: 2006 Sales: Abbott \$0.77 Billion</p> <p>Profile: A cephalosporin antibiotic used to treat mild to moderate bacterial infections.</p>	<p>50 Altace</p> <p>2005 Rank: 50</p> <p>Company: 2006 Sales: King \$0.72 Billion</p> <p>Profile: An ACE inhibitor used to treat hypertension and heart disease.</p>	<p>51 OxyContin</p> <p>2005 Rank: 24</p> <p>Company: 2006 Sales: Purdue \$0.88 Billion</p> <p>Profile: An opioid analgesic used to treat moderate to severe pain.</p>	<p>52 Lyrica</p> <p>2005 Rank: N/A</p> <p>Company: 2006 Sales: Pfizer \$0.88 Billion</p> <p>Profile: An anticonvulsant used to treat pain and seizures.</p>
<p>Actiq</p> <p>Company: 2006 Sales: Amgen \$0.78 Billion</p>	<p>69 Depakote</p> <p>Company: 2006 Sales: Abbott \$0.77 Billion</p>	<p>70 Combivent</p> <p>Company: 2006 Sales: King \$0.72 Billion</p>	<p>71 Humalog</p> <p>Company: 2006 Sales: Purdue \$0.88 Billion</p>	<p>72 Geodon</p> <p>Company: 2006 Sales: Merck \$1.15 Billion</p>

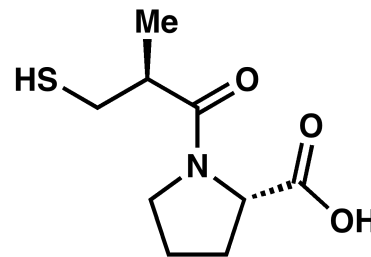
Angiotensin-Converting-Enzyme inhibitor



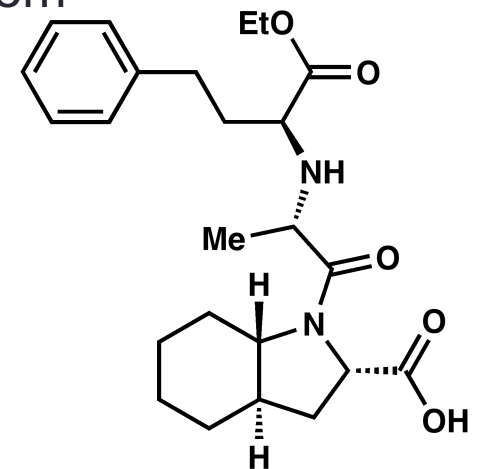
Renin-angiotensin-aldosterone system



ramipril



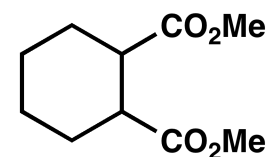
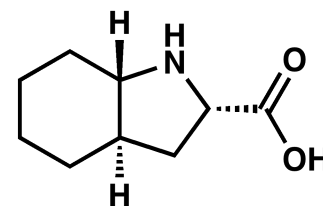
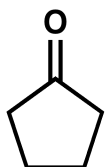
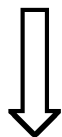
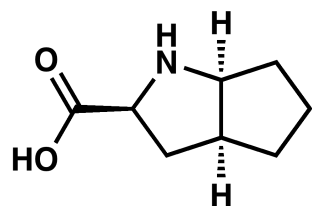
catopril



trandolopril

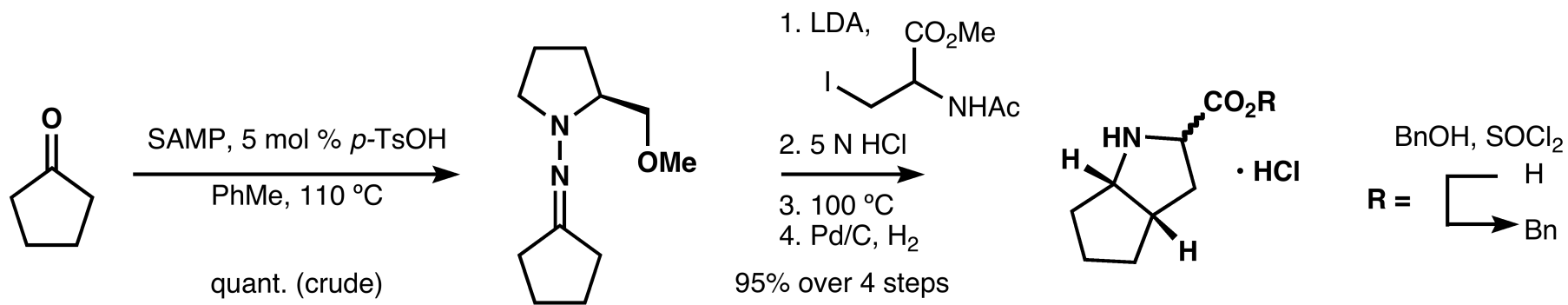
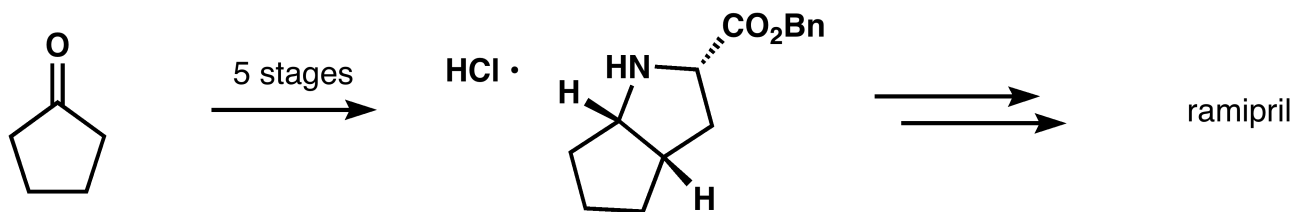
ACE inhibitor. (2012, May 8). In *Wikipedia, The Free Encyclopedia*.

Retro Synthesis



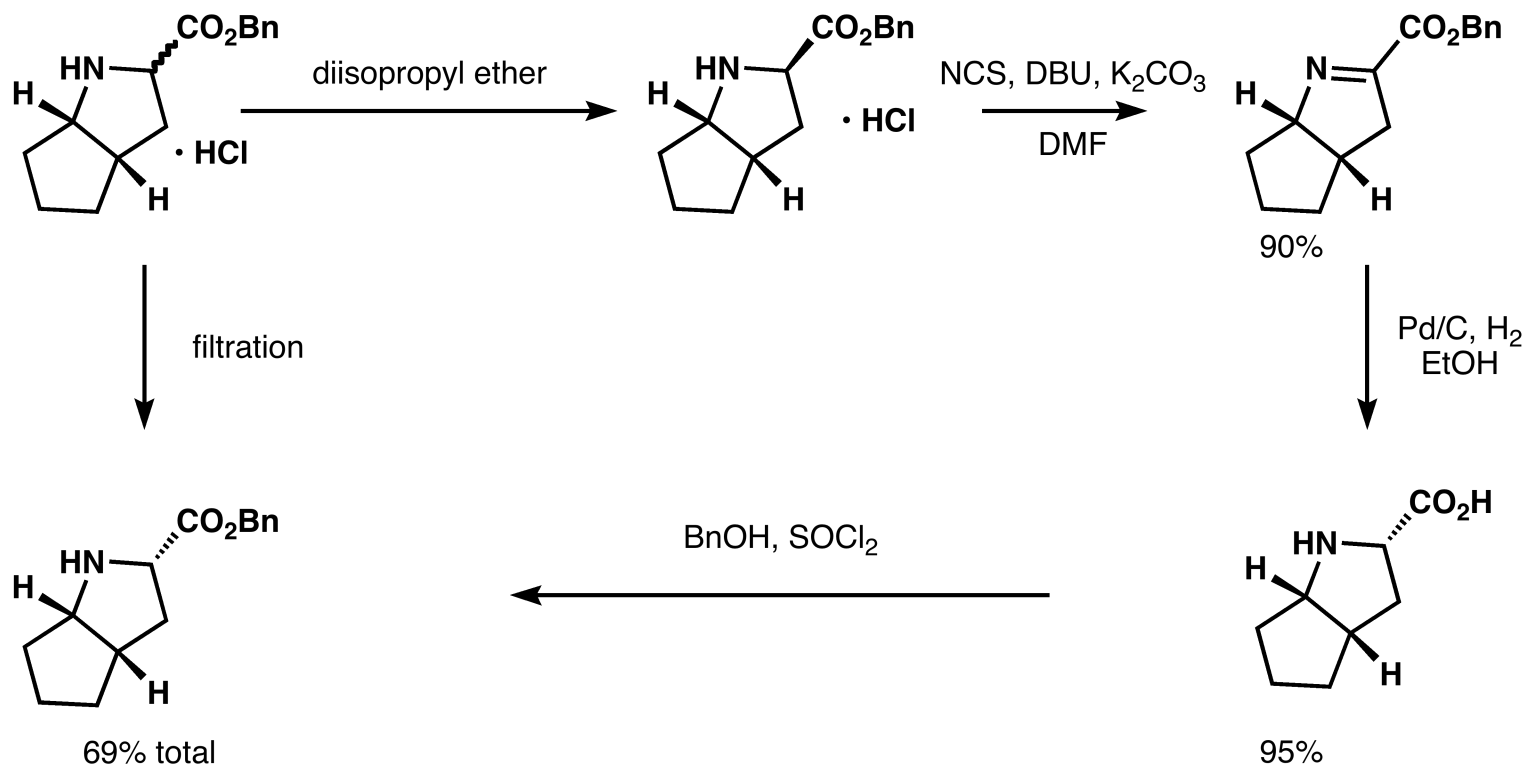
Need for cheap and scalable enantioselective processes

Ramipril (Altace)

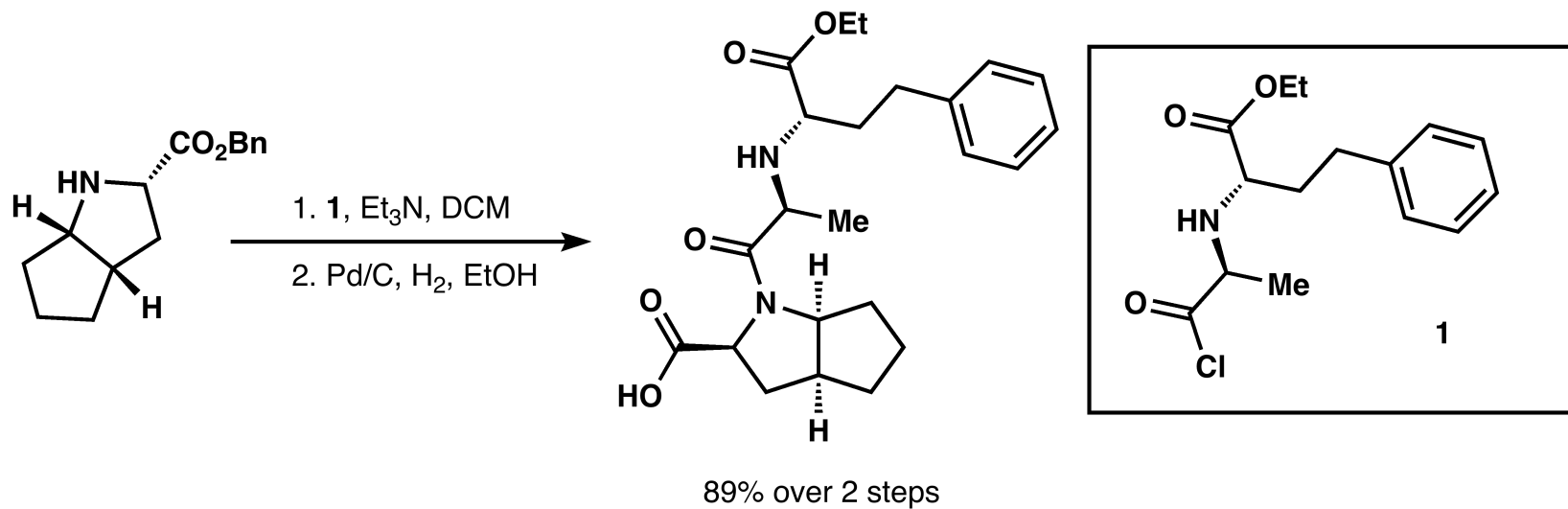


SAMP = (S)-1-amino-2-methoxymethylpyrrolidine

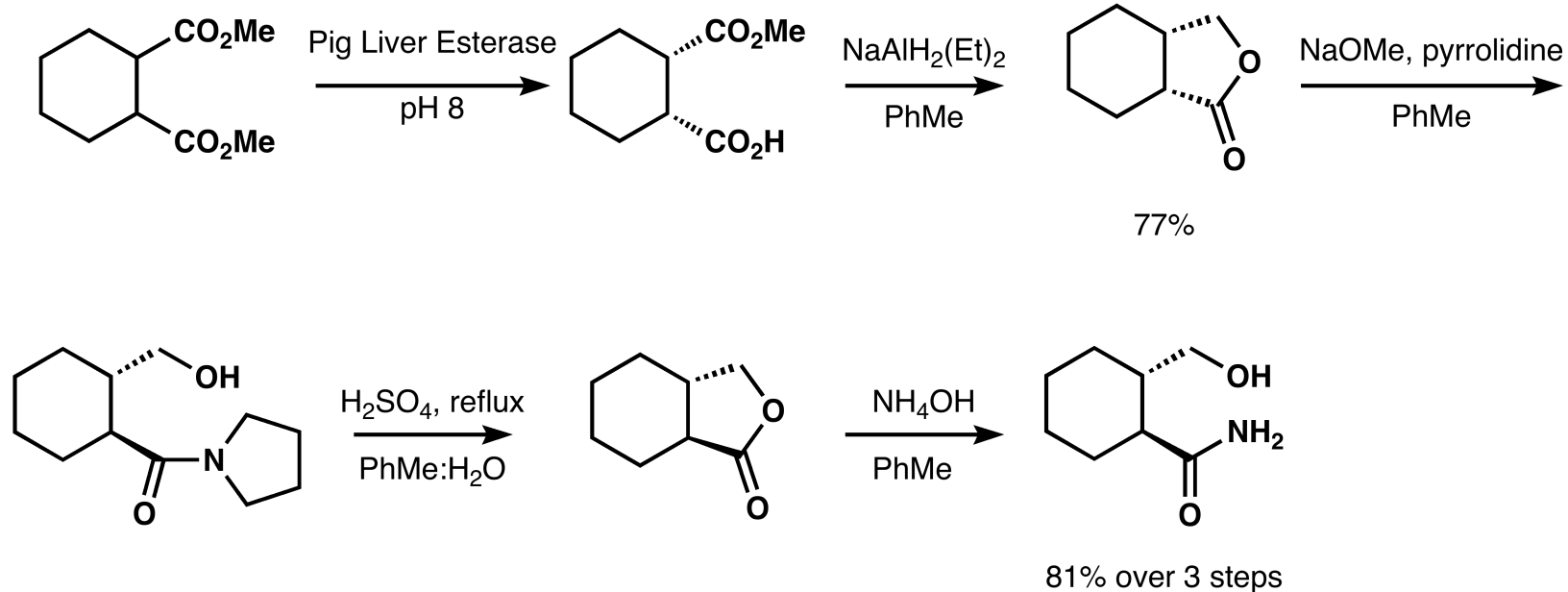
Ramipril



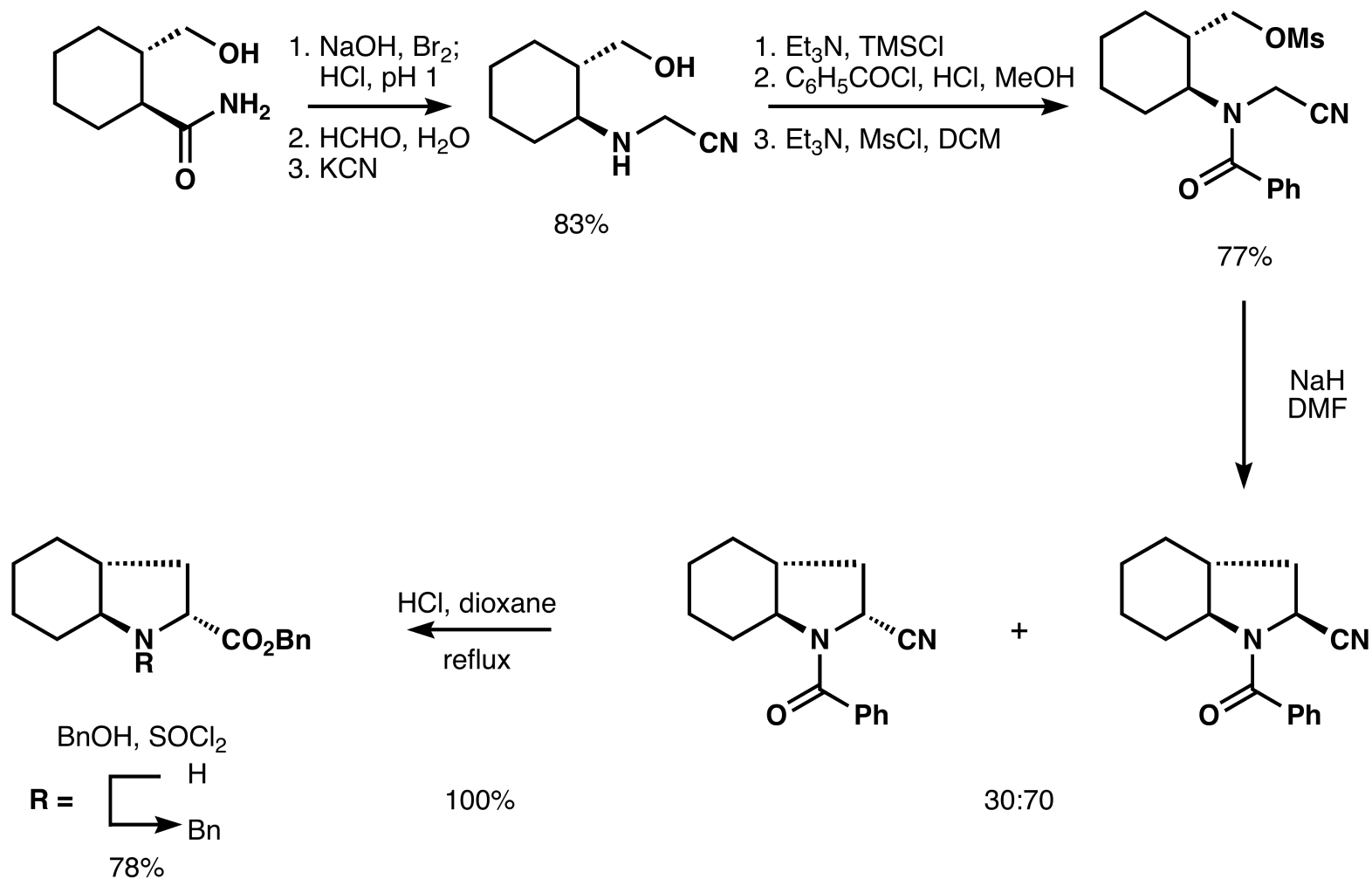
Ramipril



Trandolapril (Mavik)

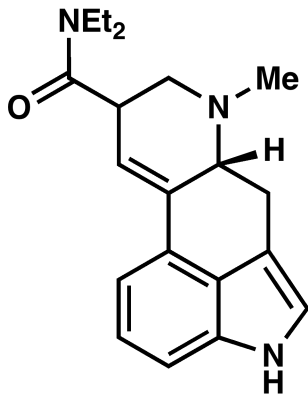


Trandolapril

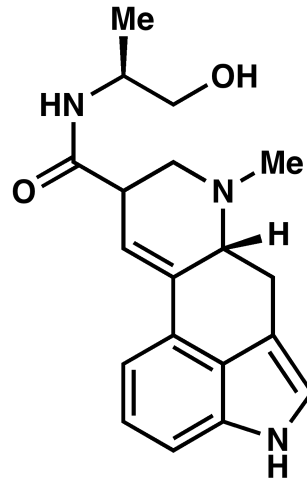


Ergot Alkaloids

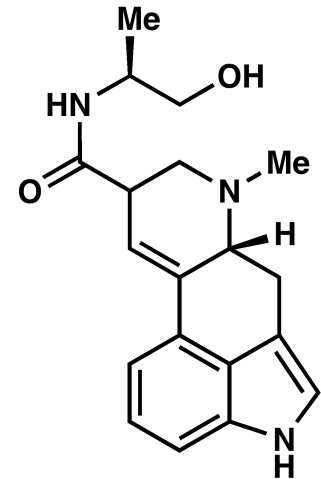
Activity in muscular, vascular and central nervous systems, and nicotinic acetylcholine receptors



LSD

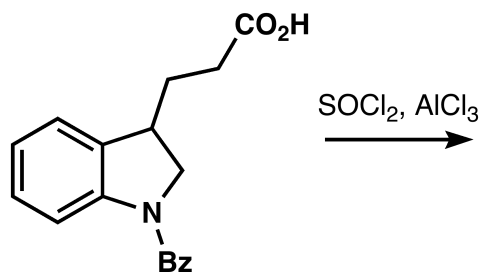


ergometrine

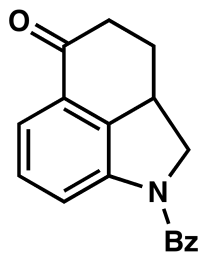


methysergide

Woodward Synthesis of Lysergic Acid

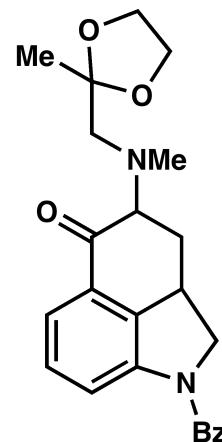
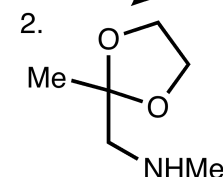


SOCl₂, AlCl₃



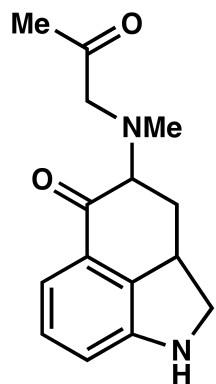
77%

1. Br₂, pyr



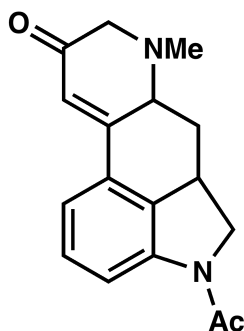
55%

6 N HCl



1. NaOMe, EtOH

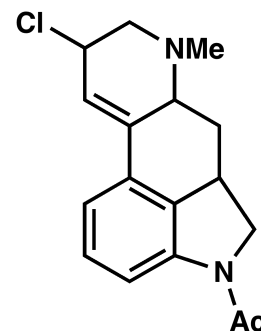
2. Ac₂O



43%

1. NaBH₄

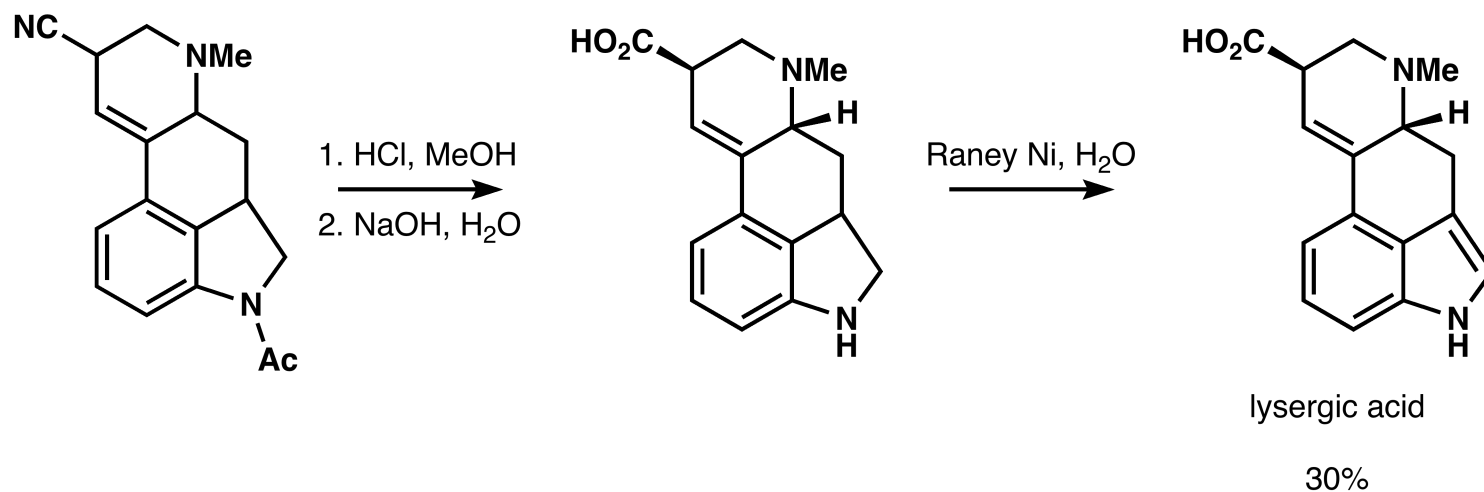
2. SOCl₂, SO₂



90%

NaCN, HCN

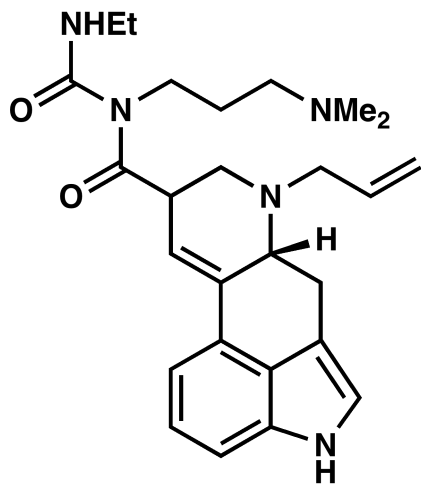
Woodward Synthesis of Lysergic Acid



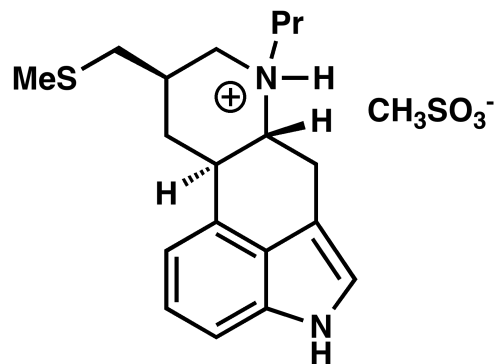
Environmentally Friendly Syntheses

Dopamine Receptor Agonists

Used in the treatment of low dopamine conditions.

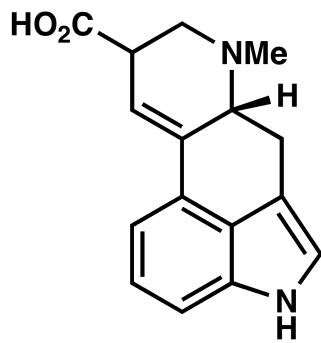


cabergoline

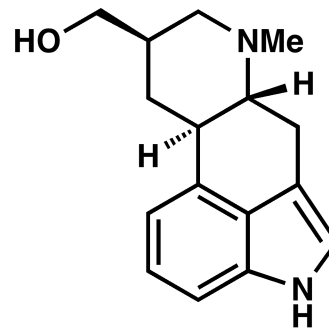
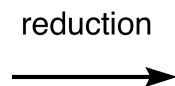


pergolide mesylate

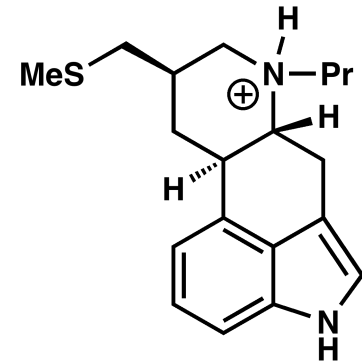
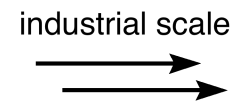
Pergolide (Permax)



lysergic acid

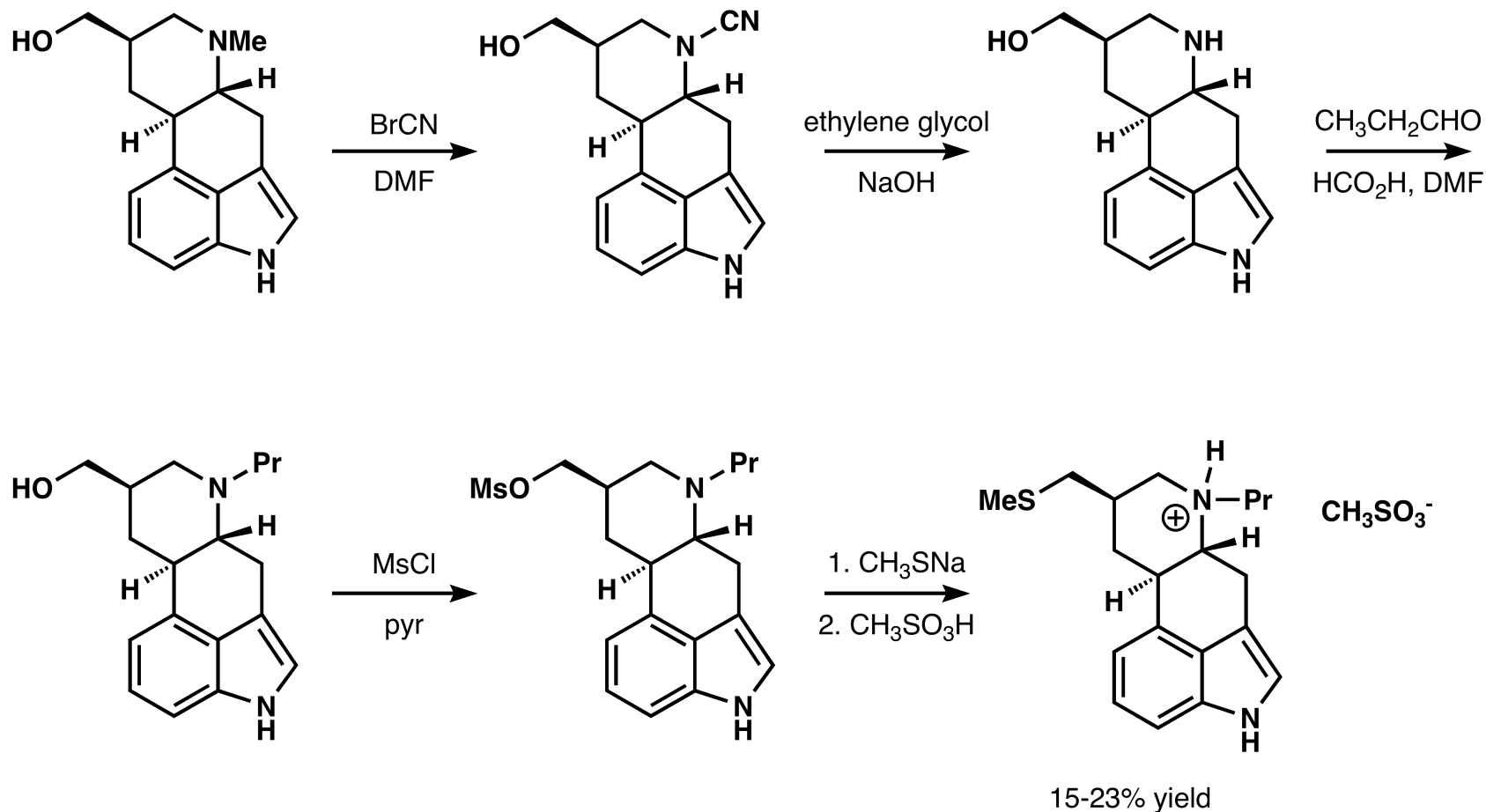


dihydrosergol

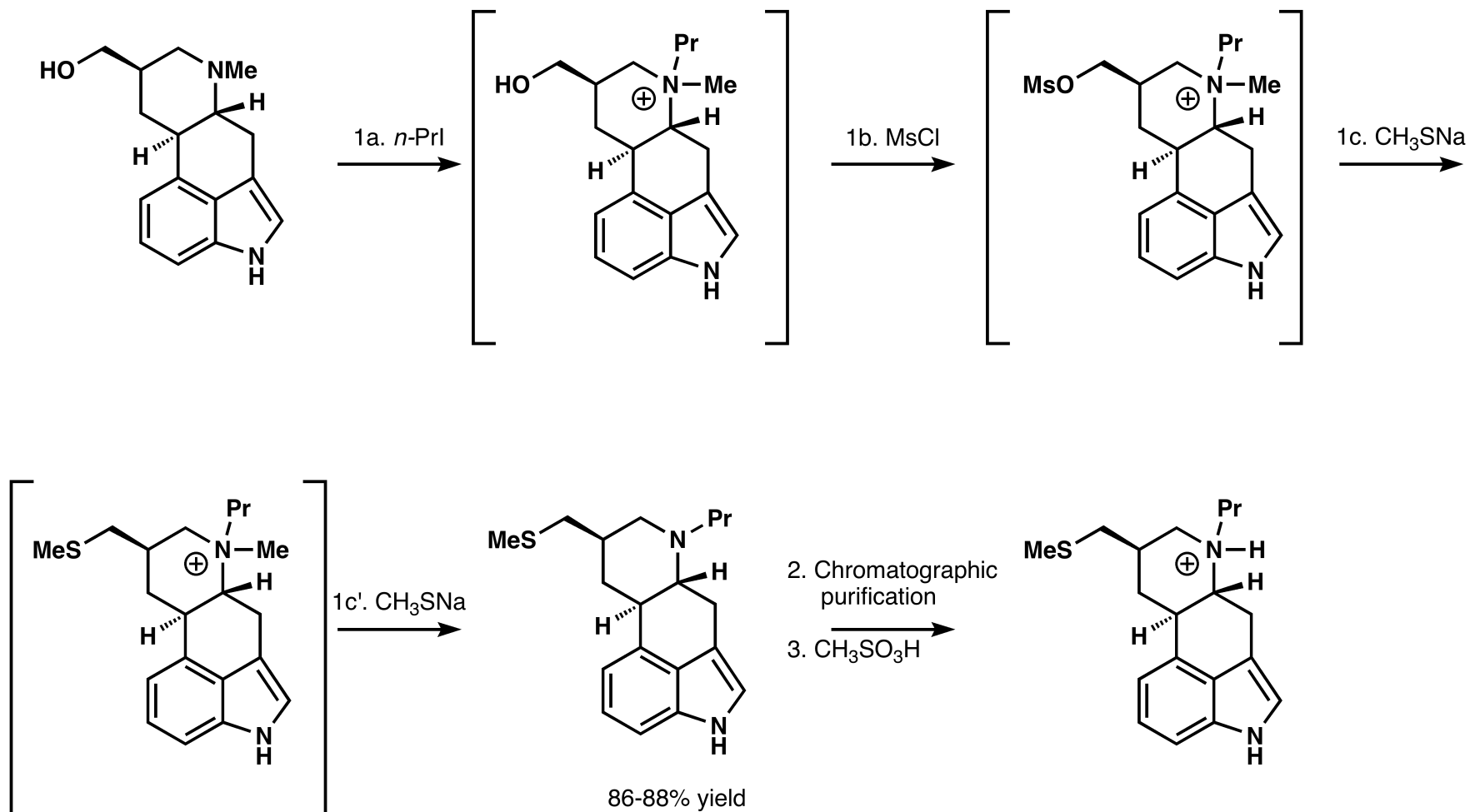


pergolide (Permax)

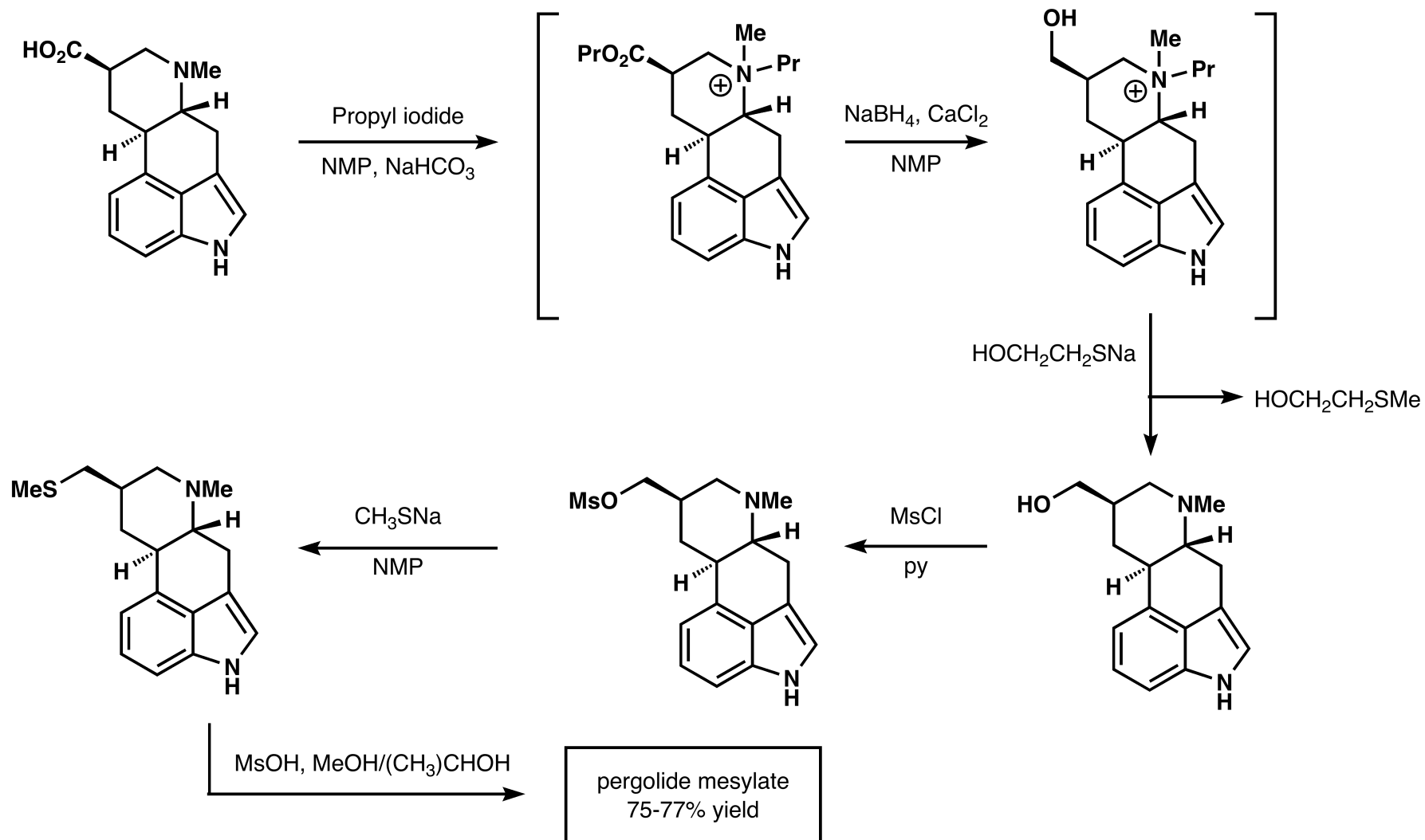
Korfeld/Bach Process



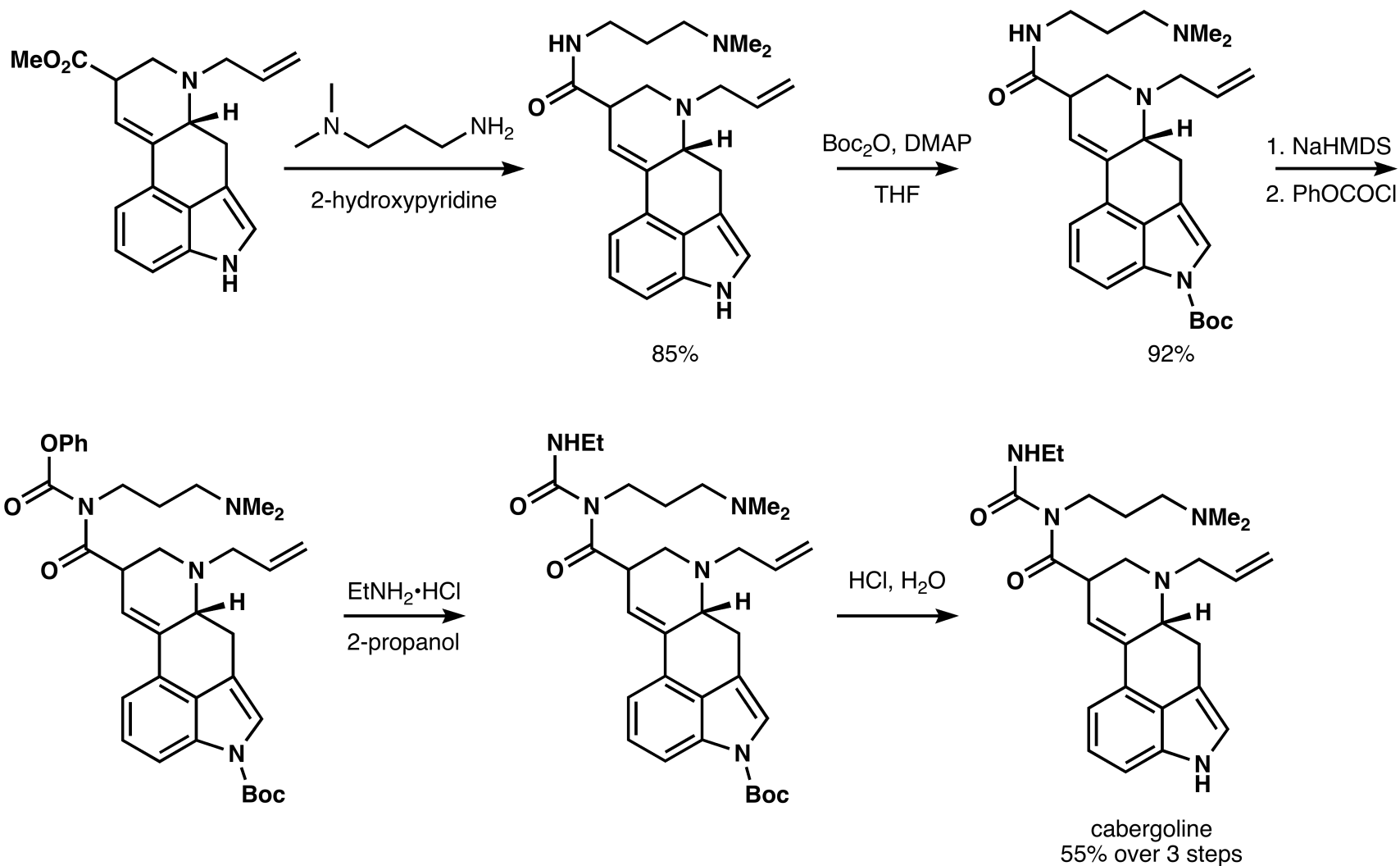
Misner Process



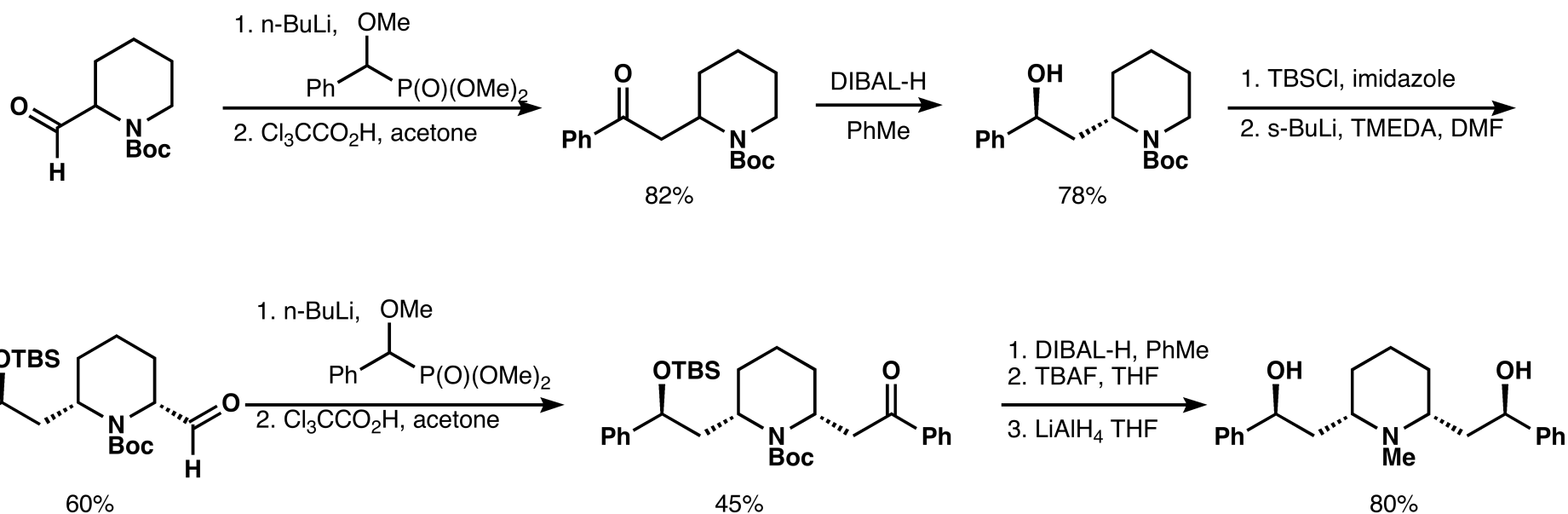
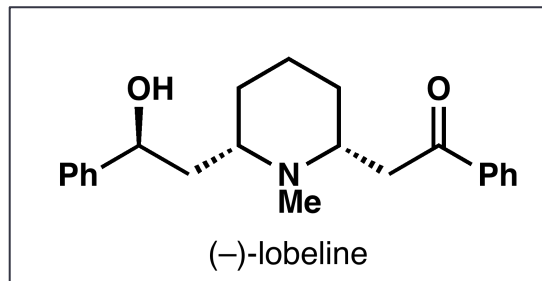
Antibiotics Process



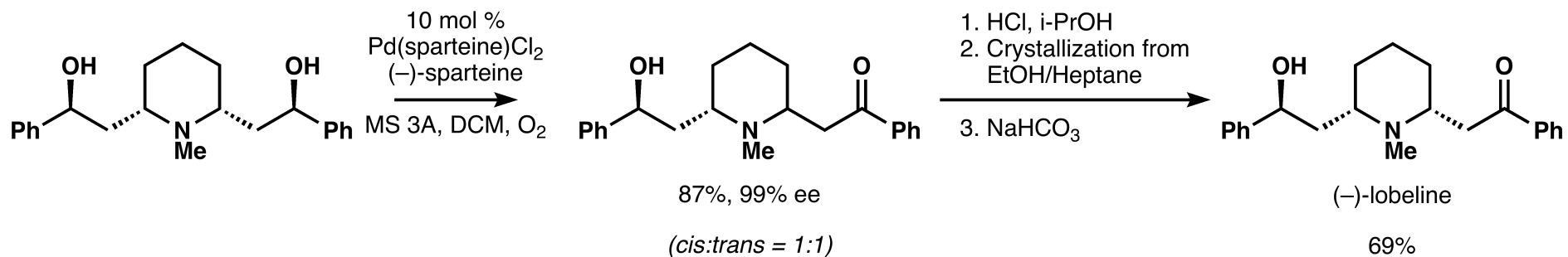
Cabergoline (Dostinex/Cabaser)



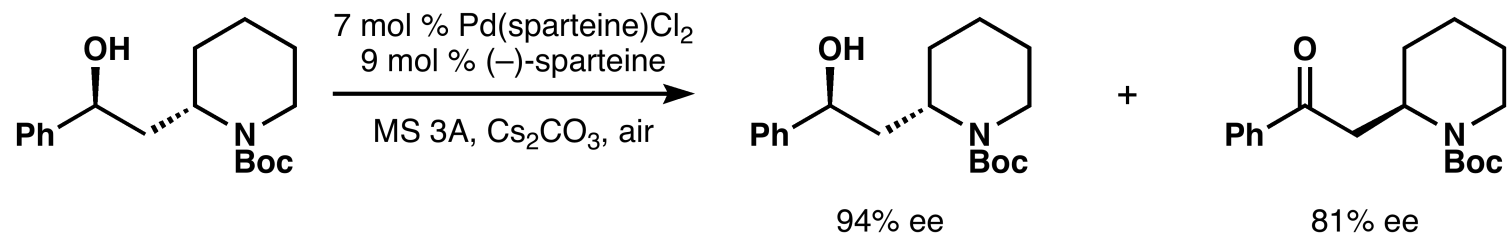
Lobeline



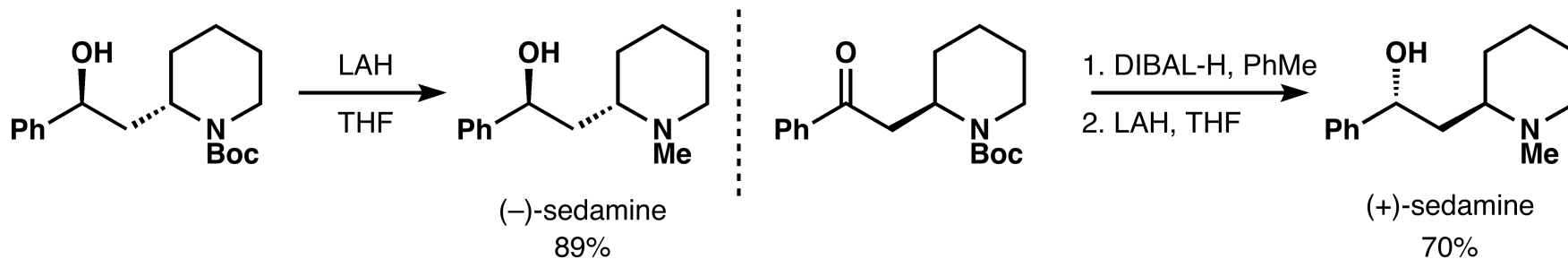
Lobeline



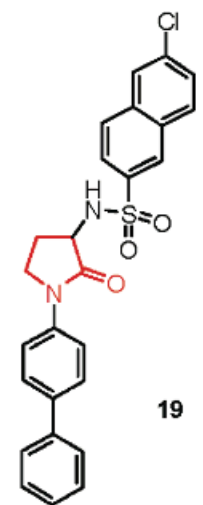
Sedanine



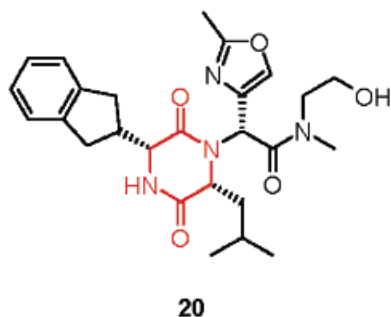
53.8% conversion
98% combined isolated yield



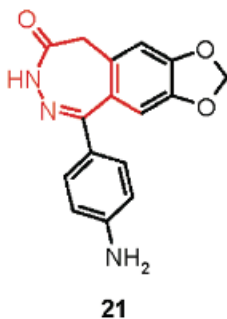
Conclusion



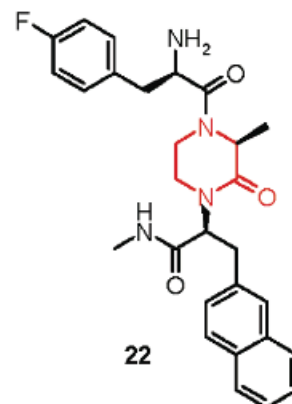
Factor Xa Inhibitors
GSK



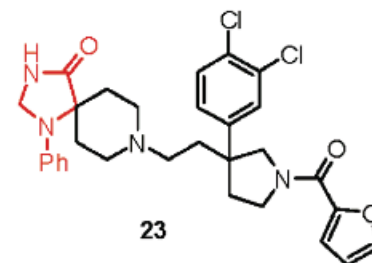
Oxytocin antagonist
GSK



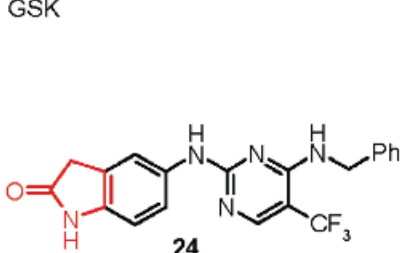
AMPA Antagonists
Pfizer



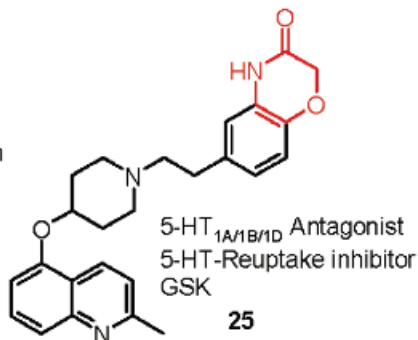
Melanocortin-4 Agonist
GSK



CCR5 ligands
GSK



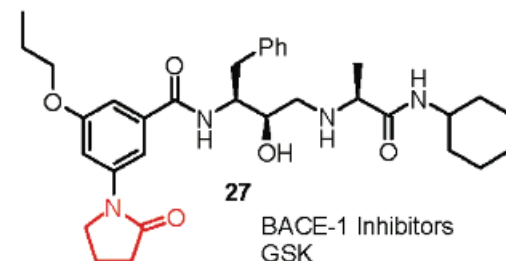
PYK2 Kinase inhibitor
Pfizer



5-HT_{1A/1B/1D} Antagonist
5-HT-Reuptake inhibitor
GSK



α 4 β 7 MAdCAM
Pfizer/Millennium



BACE-1 Inhibitors
GSK