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Best Selling Drugs

17.02.2014

Outline

- Introduction
 - Drugs against:
 - . Depression
 - . Cardiovascular disease
 - . Gastrointestinal disorders
 - . Erectile dysfunction
 - . Cancer
 - . Infections
 - . Pain
 - Summary / Conclusions
-

Introduction

Drugs in numbers_(Q4 2013):^[1]

- Drugs in the top 100:

No.	Disease	Nos. Drugs
1	Cardiovascular d.	12
2	Diabetis	11
3	Astma	9
4	Reuhm. Arthritis	7
5	Anti infectives	7
6	Pain	6
7	Depression	5
8	MS	5
9	Cancer	5
10	ADS	5

- Top 10 Drugs in Sales:

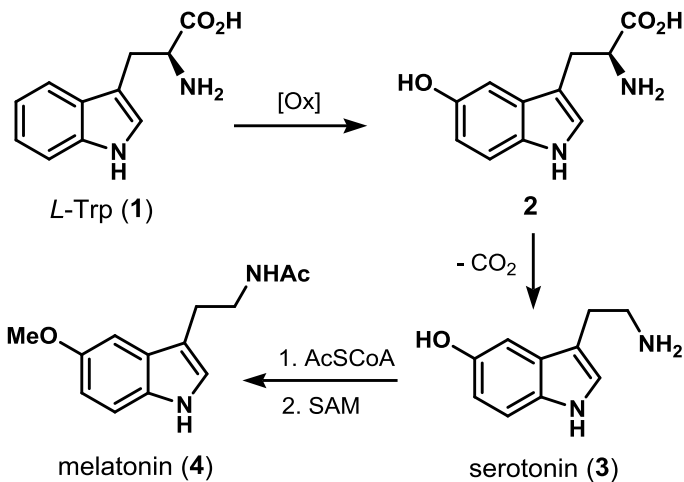
No.	Brand Name	Med. use	Sales mill.\$
1	Abifily	Depression	1.602
2	Nexium	G.I.	1.536
3	Humira	Reuhm. A.	1.462
4	Crestor	CD	1.334
5	Advair Diskus	Astma	1.247
6	Enbrel	Reuhm. A.	1.189
7	Cymbalta	Depression	1.064
8	Remicade	Reuhm. A.	994
9	Neulasta	Neutropenia	855
10	Copaxone	MS	851

[1] www.drugs.com

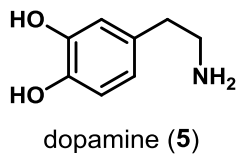
CNS drugs (mental dysfunction)

Principles:

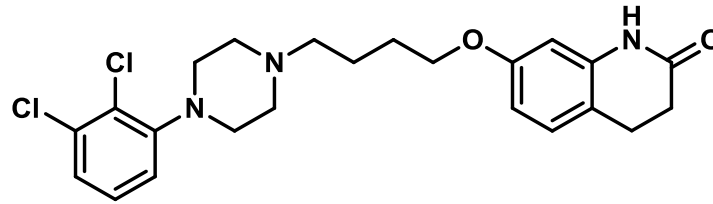
„The serotonin approach“



„The dopamine approach“



CNS drugs (mental dysfunction)



aripiprazole (6)

Substance name: Aripiprazole

Brands name: Abifily

Company: Otsuka Pharmaceutical Co.

Medical use: Schizophrenia, bipolar disorder

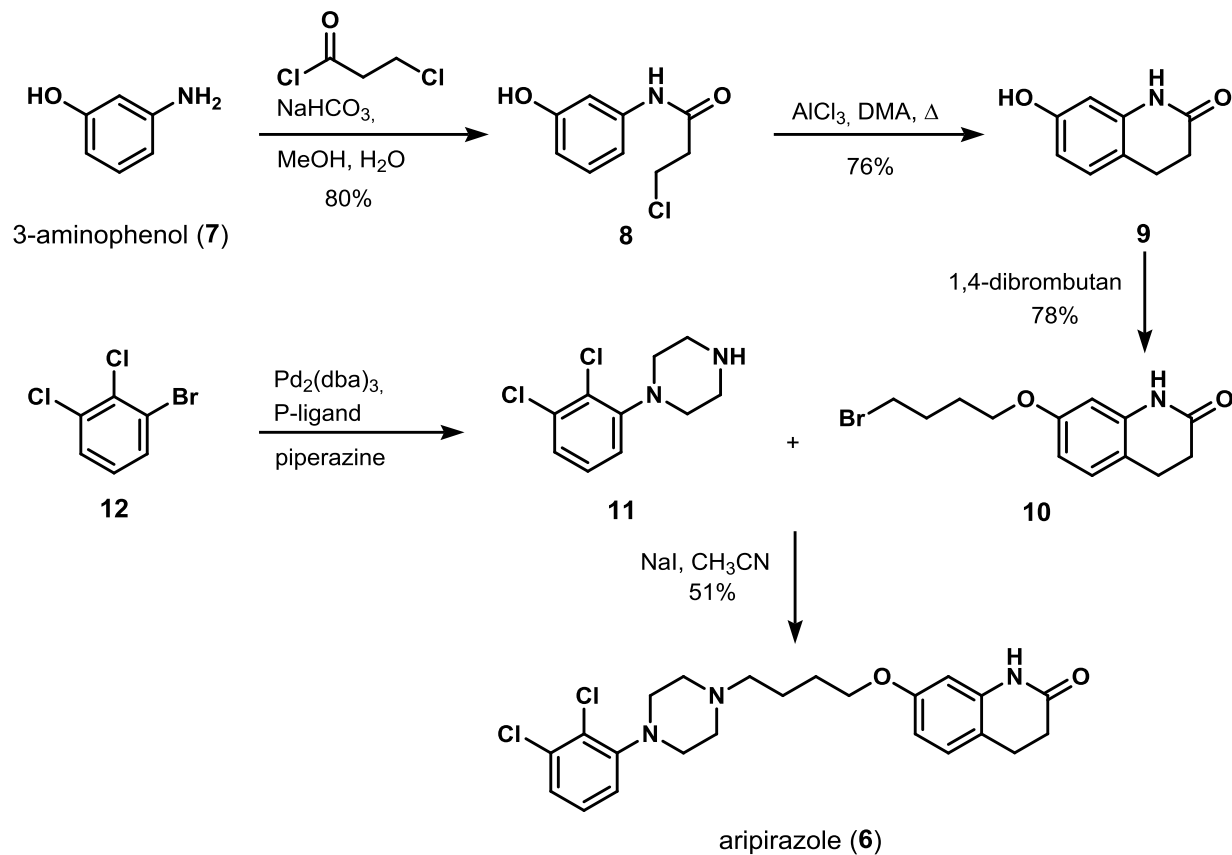
Mode of Action: Dopamine agonist

Rank_(Q4, 2013): 1

Sales_(Q4, 2013): 1,6 bill.US\$

Drug synthesis

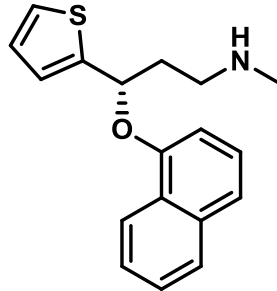
Synthesis of aripirazole:^{[2],[3]}



[2] Yasuo Oshiro et al. *J. Med. Chem.* **1998**, 41, 658

[3] US Pat. No. 5,006,528

CNS drugs (mental dysfunction)



duloxetine (15)

Substance name: Duloxetine

Brands name: Cymbalta

Company: Eli Lilly and Co.

Medical use: Depressive disorder

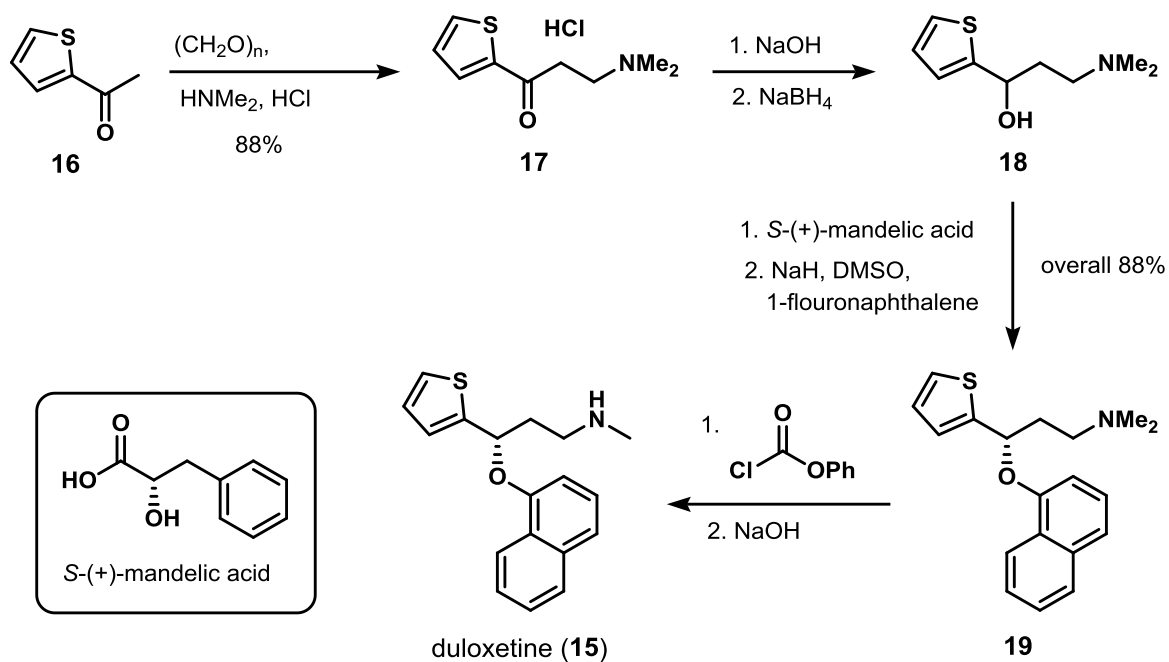
Mode of Action: Serotonine-norephinephrine reuptake inhibitor (SNRI)

Rank_(Q4, 2013): 7

Sales_(Q4, 2013): 1,06 bill.US\$

Drug synthesis

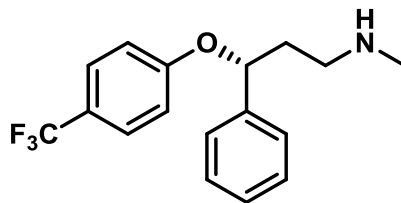
Synthesis of duloxetine:[4],[5]



[4] Pat. No.: US20090221668 A1, EP1971592 B1

[5] L. Weigl et al. *Tetrahedron Lett.* **1990**, 7101

CNS drugs (mental dysfunction)



fluoxetine (20)

Substance name: Fluoxetine

Brands name: Prozac

Company: Eli Lilly and Co.

Medical use: Depressive disorder

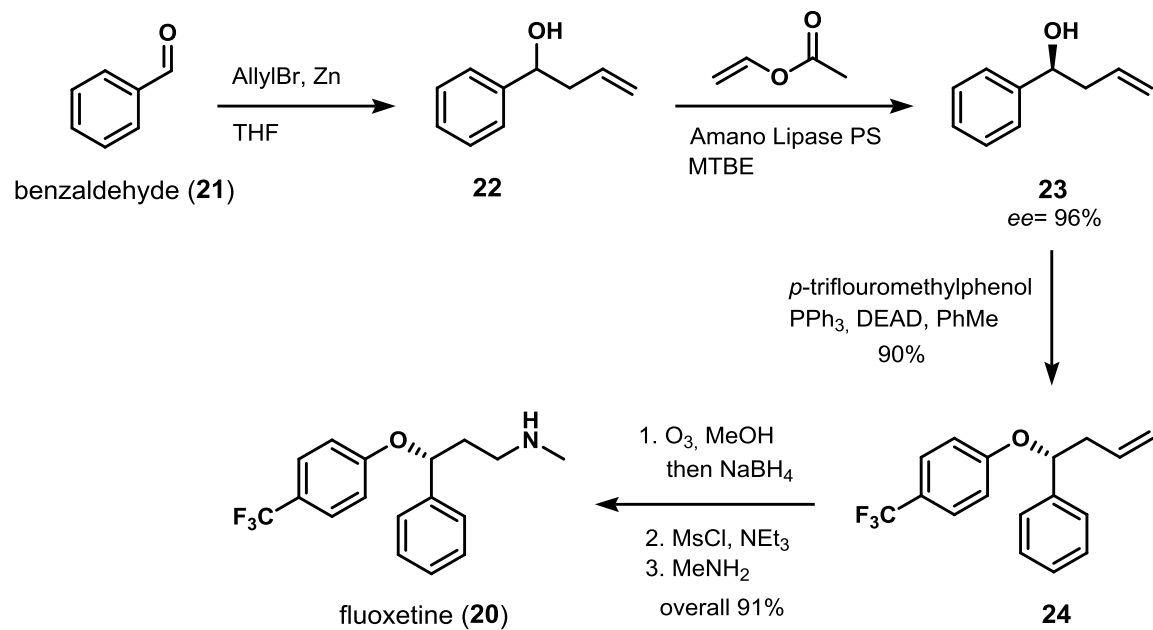
Mode of Action: Serotonine reuptake inhibitor (SSRI)

Rank_(Q4, 2013): n/a

Sales_(Q4, 2013): n/a

Drug synthesis

Synthesis of fluoxetine:^{[6],[7]}



[6] F. Bacher *et al. Bioorg Med. Chem.* **1996**, 6, 877

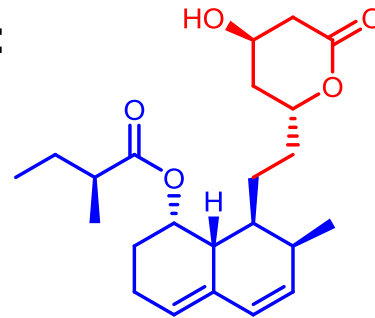
[7] D. W. Robertson *et al. J. Med. Chem.* **1988**, 31, 1412

CD drugs

Mode of Action:

Isolation of compactin in 1976:

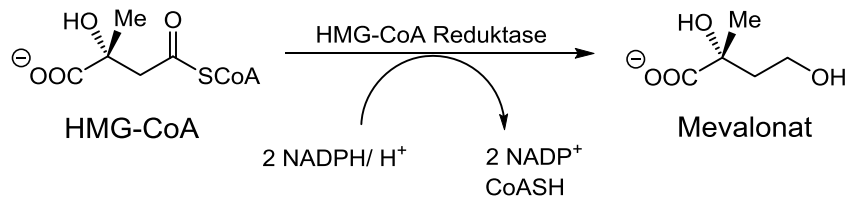
- Metabolite of *Penicillium Brevicompactum*, isolated from Braun *et al.* [8]



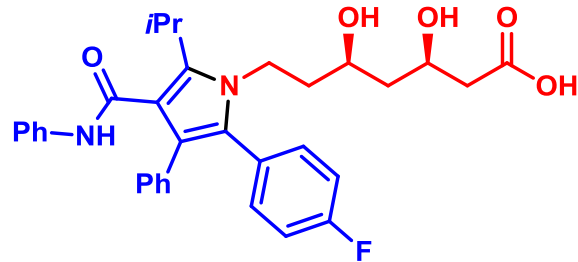
compactin (25)

Biological activity:

- Inhibition of the HMG-CoA reductase



CD drugs



atorvastatin (26)

Substance name: Atorvastatin

Brands name: Lipitor

Company: Pfizer

Medical use: Treatment of dyslipidemia

Mode of Action: HMG-CoA reductase inhibitor

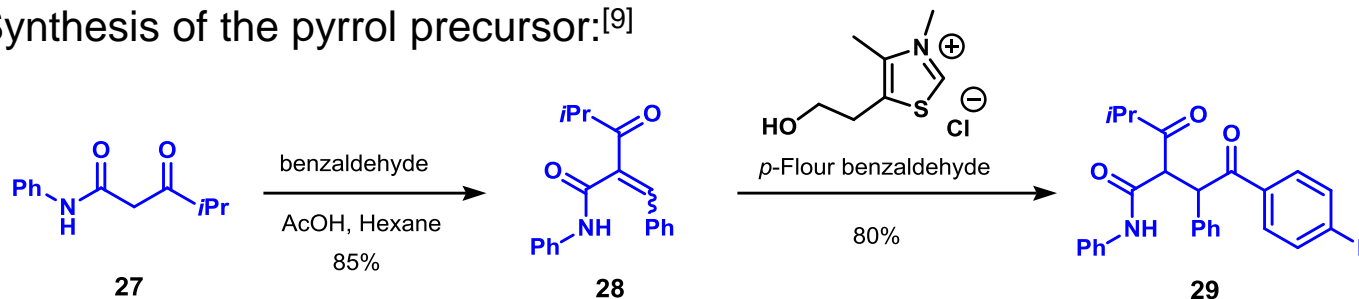
Rank_(Q2, 2013): 99

Sales_(Q2, 2013): 170 mill.US\$

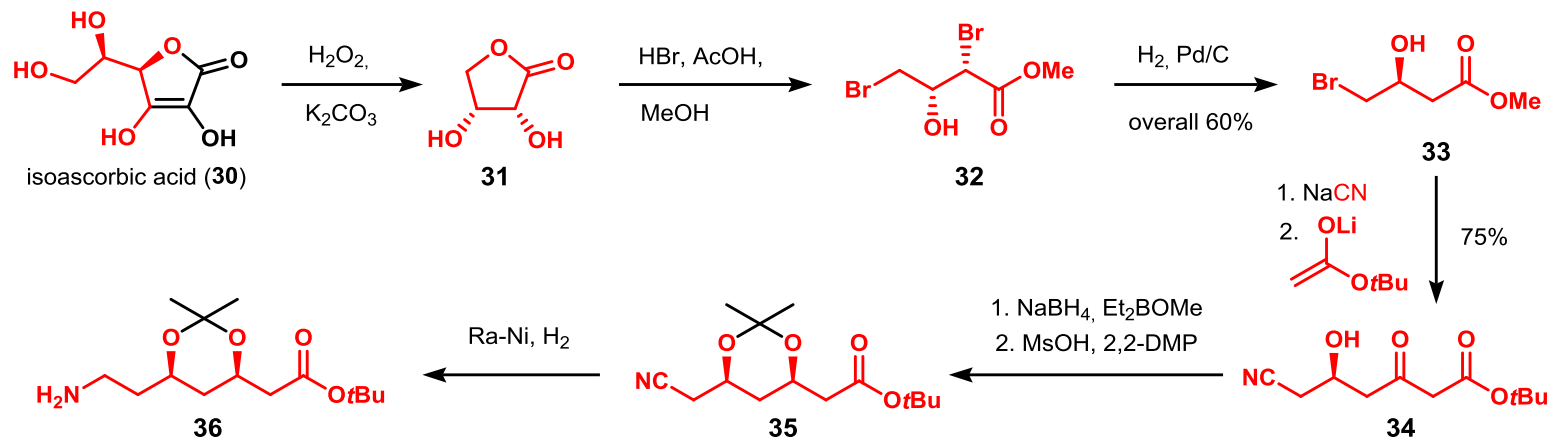
Drug synthesis

Synthesis of atorvastatin:

- Synthesis of the pyrrol precursor:[9]



- Synthesis of the side chain:[9],[10]

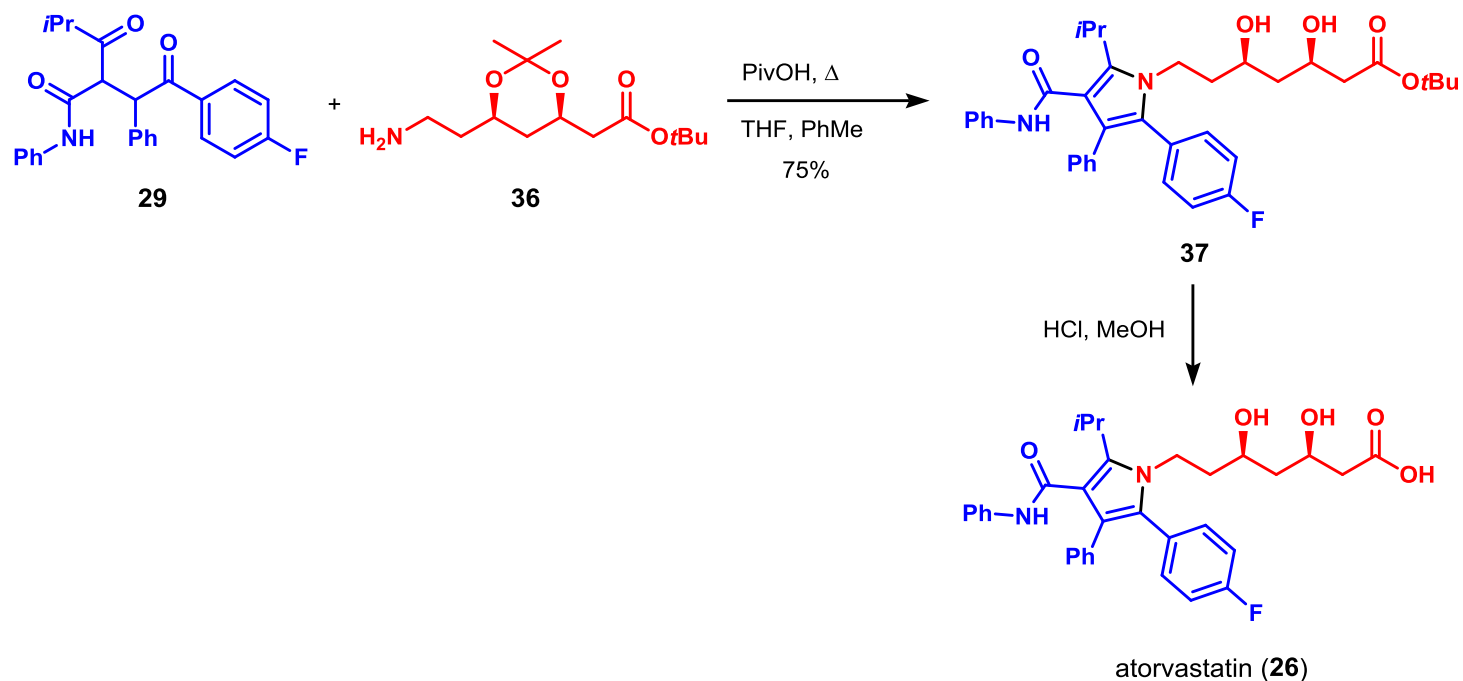


[9] US Pat. Nos. 5,124,482; 5,216,174 and 5,273,995

[10] N. Cohen et. al. *J. Am. Chem. Soc.* **1983**, 105, 3661 and OS **1985**, Vol. 63, p127

Drug synthesis

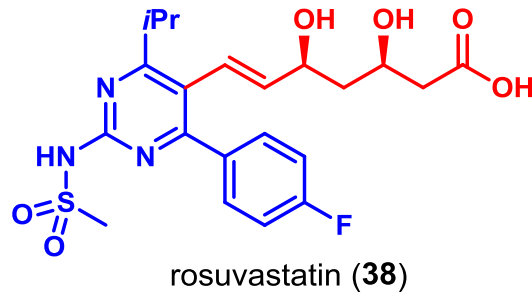
Synthesis of atorvastatin:^{[11],[12]}



[11] B.D. Roth et al. *J. Med. Chem.* **1991**, 34, 357

[12] Pat. No.: EP2240442 B1

CD drugs



Substance name: Rosuvastatin

Brands name: Crestor

Company: AstraZeneca Pharmaceuticals

Medical use: Treatment of dyslipidemia

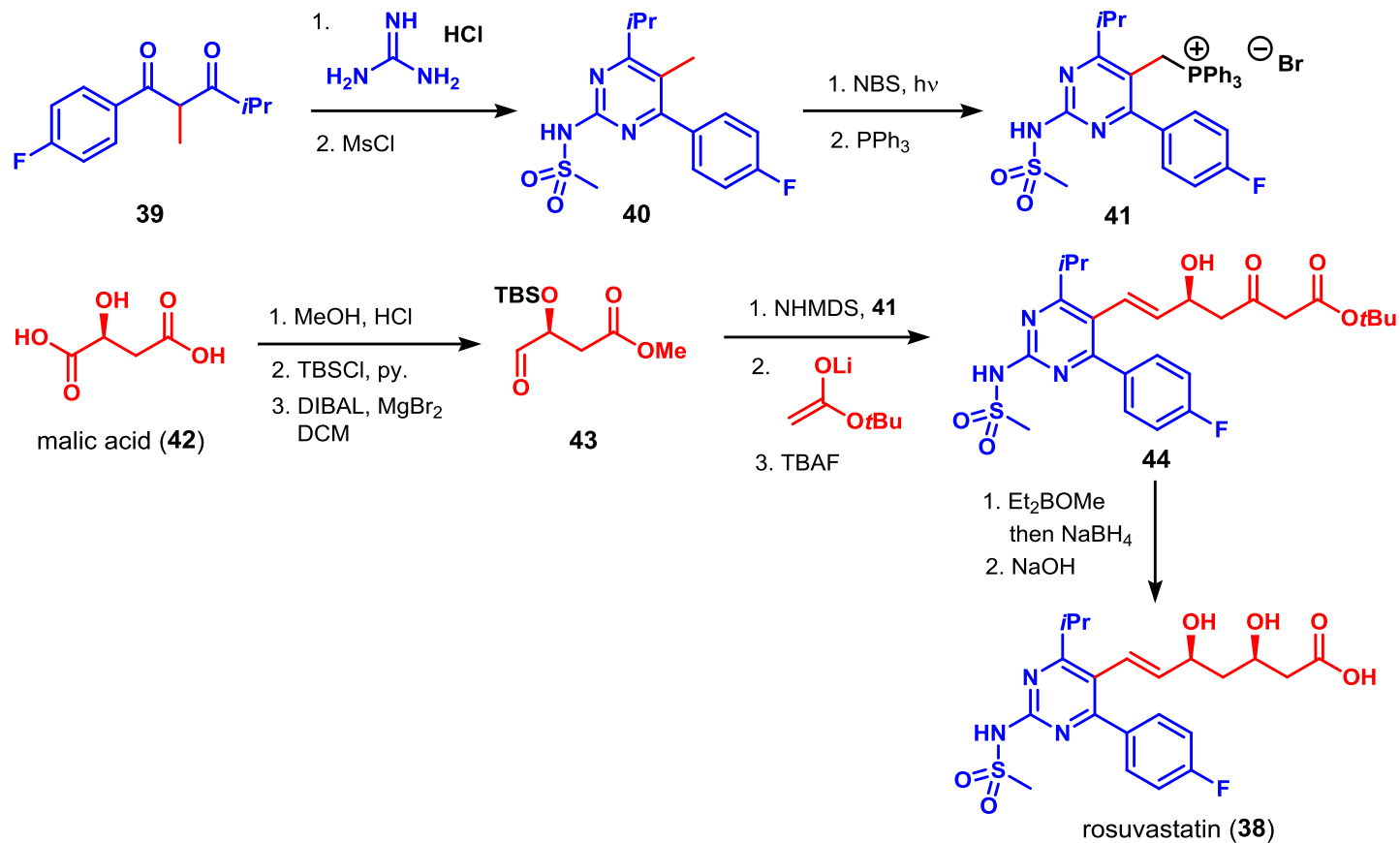
Mode of Action: HMG-CoA reductase inhibitor

Rank_(Q4, 2013): 4

Sales_(Q4, 2013): 1,3 bill.US\$

Drug synthesis

Synthesis of rosuvastatin:^{[13],[14]}

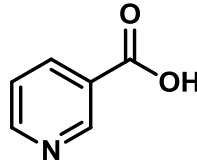


[13] Pat. No.: US20080255170 A1

[14] for a different approach see Pat. No.: US8318933 B2

[14] N. Andrushko *et al.* *Eur. J. Org. Chem.* **2008**, 847

CD drugs



niacin (45)

Substance name: Niacin

Brands name: Niaspan

Company: Abbott Laboratories

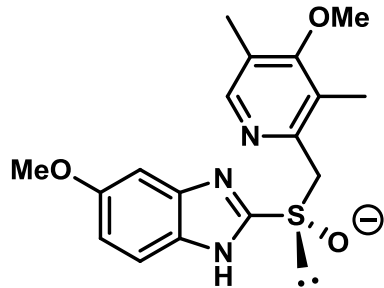
Medical use: to lower the lipid level (TG, LDL, VLDL)

Mode of Action: binding to niacin receptor 1 and 2 (NIACR1, 2)

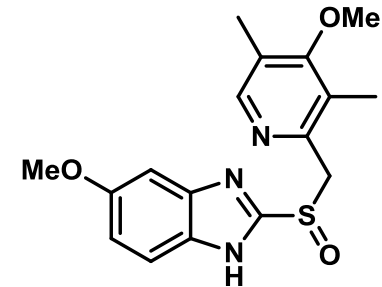
Rank_(Q3, 2013): 63

Sales_(Q3, 2013): 240 mill.US\$

Drugs for gastrointestinal disorders



esomeprazole (48)



omeprazole (49)

Substance name: Esomeprazole

Brands name: Nexium

Company: AstraZeneca Pharmaceuticals

Medical use: Dyspepsia and other disease

Mode of Action: Proton pump inhibitor

Rank_(Q4, 2013): 2

Sales_(Q4, 2013): 1,3 bill.US\$

Substance name: Omeprazole

Brands name: Prilosec

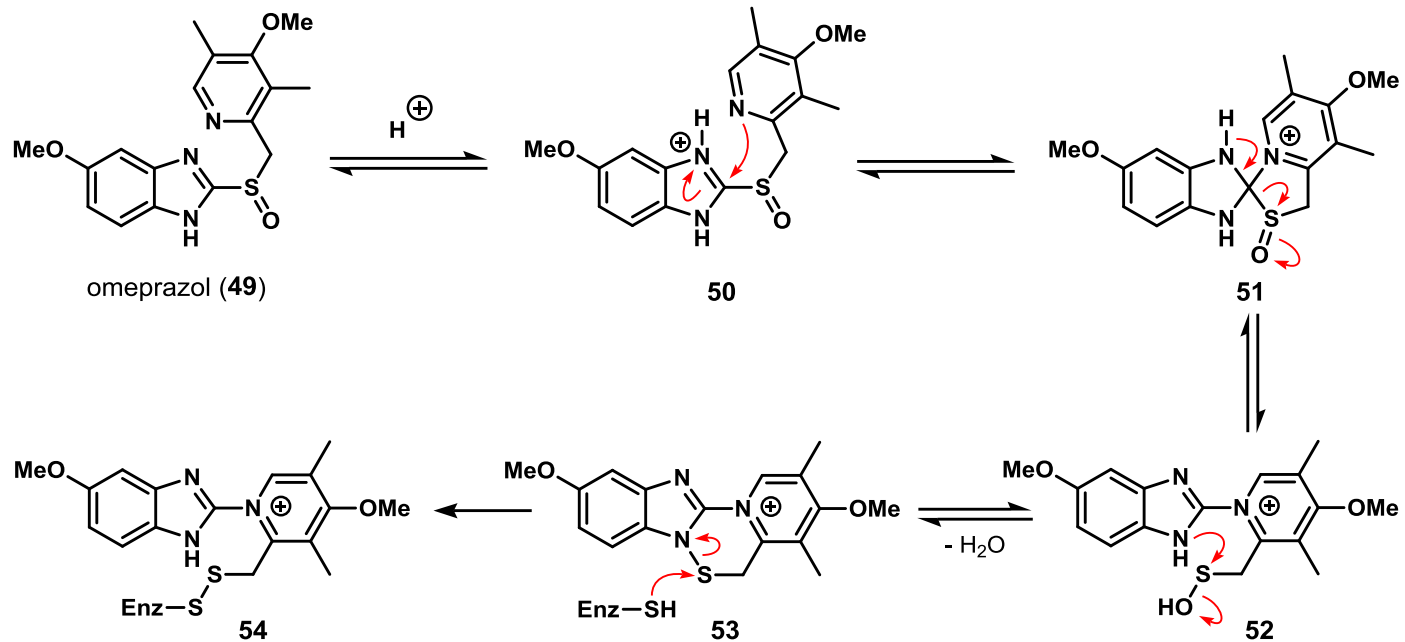
Rank_(Q2, 2013): 94

Sales_(Q2, 2013): 180 mill.US\$

Drugs for gastrointestinal disorders

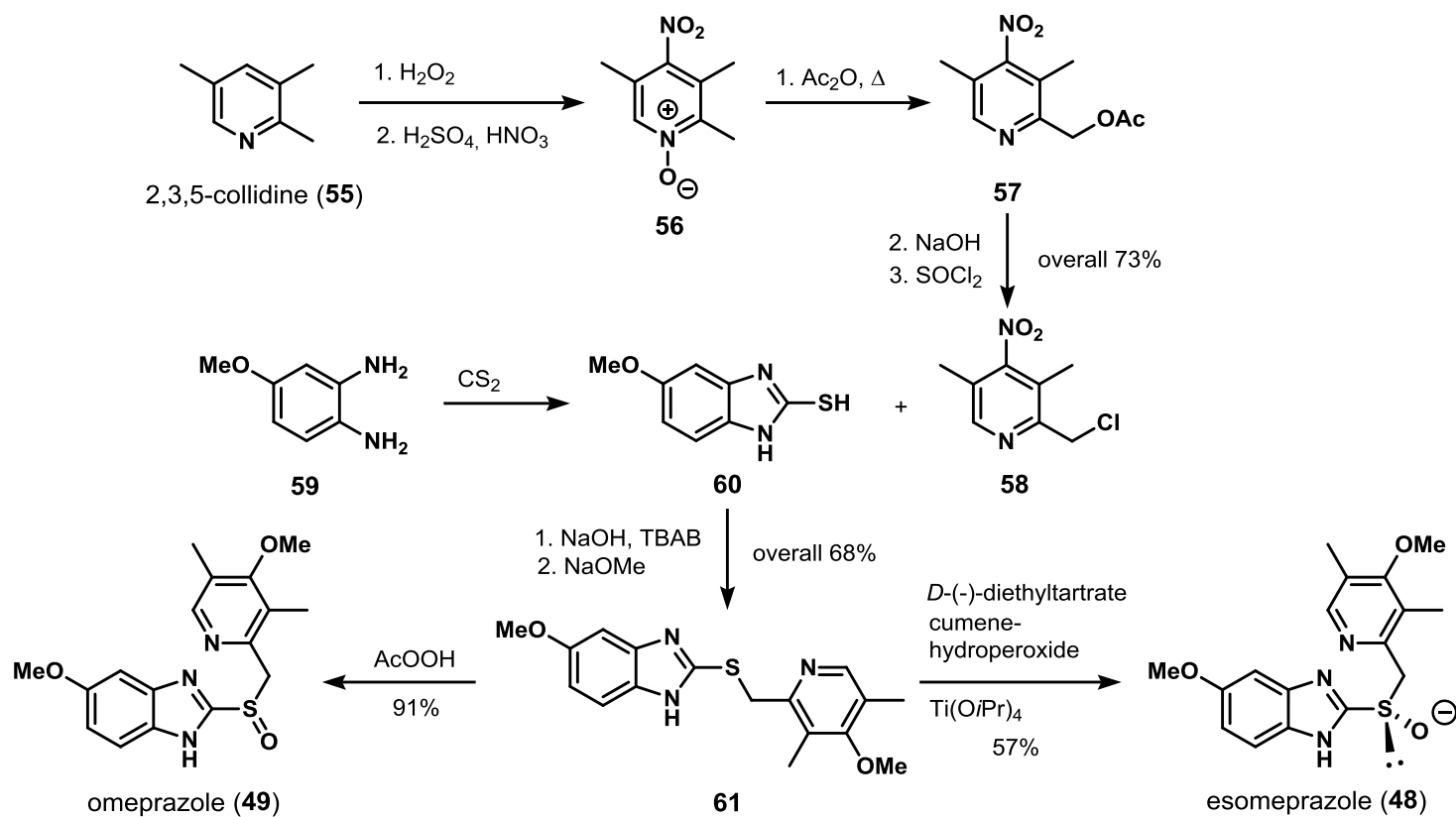
Mode of action:

The „Pro Drug“-principle:



Drug synthesis

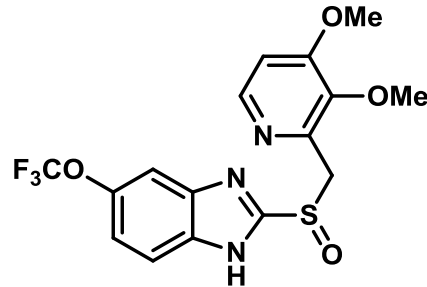
Synthesis of esomeprazole and omeprazole:^{[16],[17]}



[16] Pat. No.: EP1085019 A1

[17] Pat. No.: EP2186807 A1

Drugs for gastrointestinal disorders



pantoprazole (62)

Substance name: Pantoprazole

Brands name: Somac

Company: Wyeth-Ayerst Laboratories

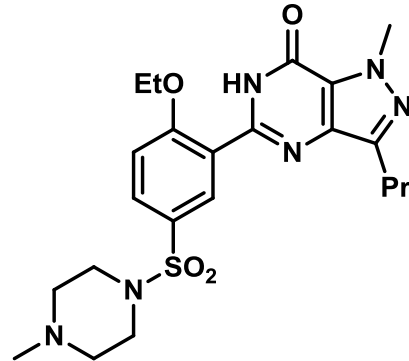
Medical use: Dyspepsia and other disease

Mode of Action: Proton pump inhibitor

Rank_(Q4, 2013): n/a

Sales_(Q4, 2013): n/a

Drugs against erectile disorders



sildenafil (65)

Substance name: Sildenafil

Brands name: Viagra

Company: Pfizer

Medical use: Erectile dysfunction

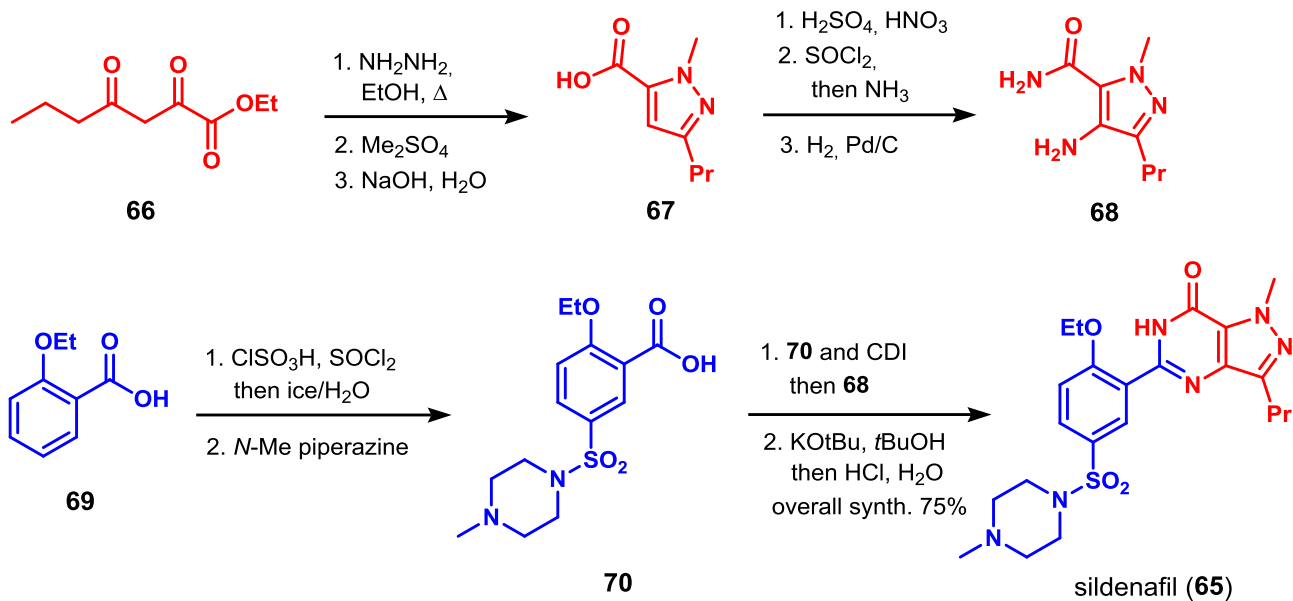
Mode of Action: Inhibits cGMP phosphodiesterase type 5 (PDE5)

Rank_(Q4, 2013): 45

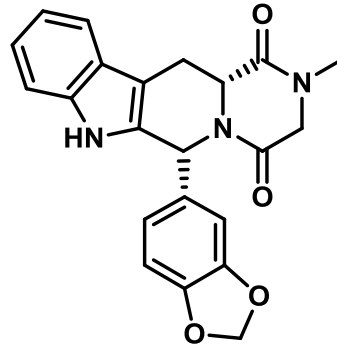
Sales_(Q4, 2013): 300 mill.US\$

Drug synthesis

Synthesis of sildenafil:^[18]



Drugs against erectile disorders



tadalafil (71)

Substance name: Tadalafil

Brands name: Cialis

Company: Eli Lilly and Co.

Medical use: Erectile dysfunction

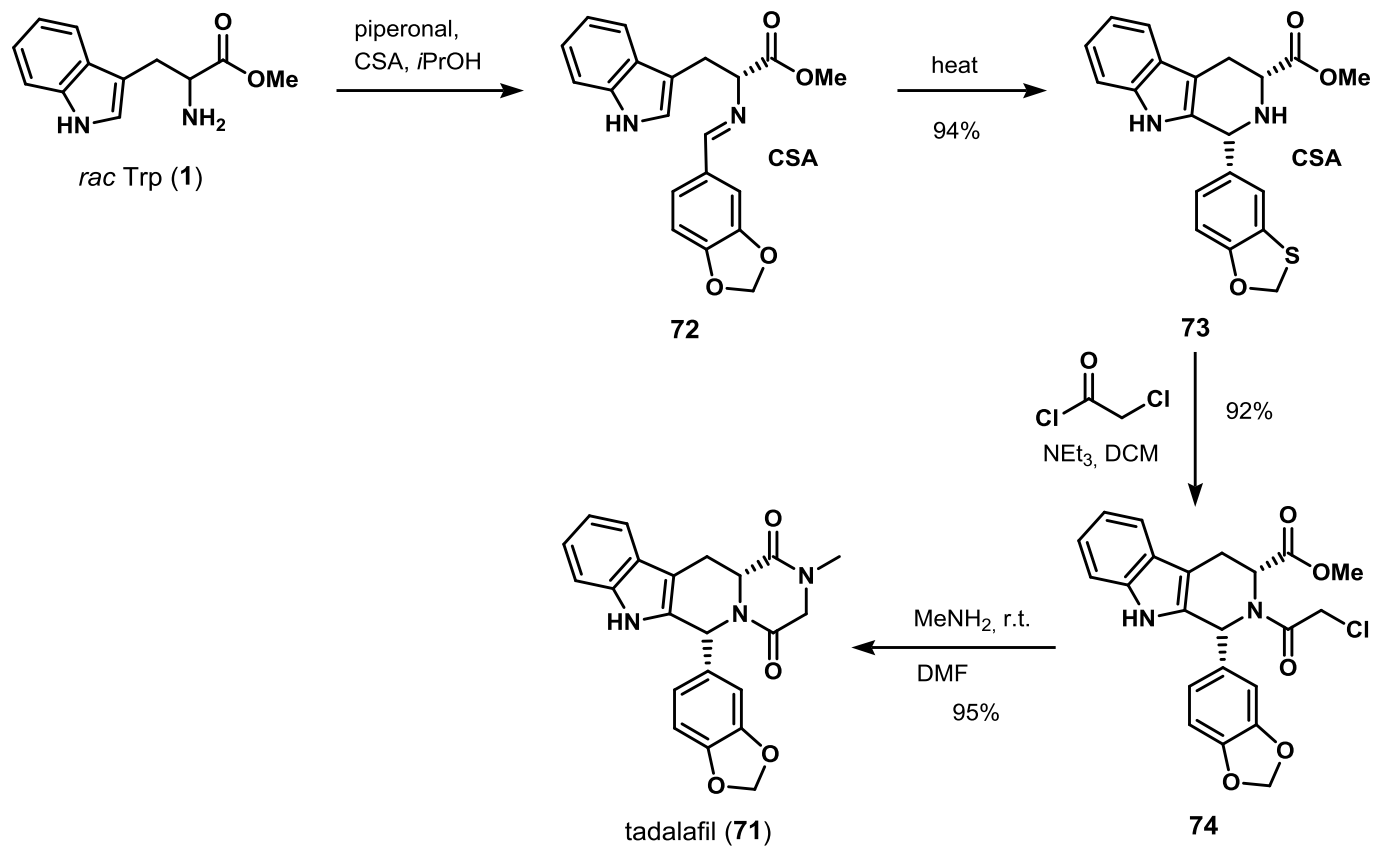
Mode of Action: Inhibits cGMP phosphodiesterase type 5 (PDE5)

Rank_(Q4, 2013): 51

Sales_(Q4, 2013): 280 mill.US\$

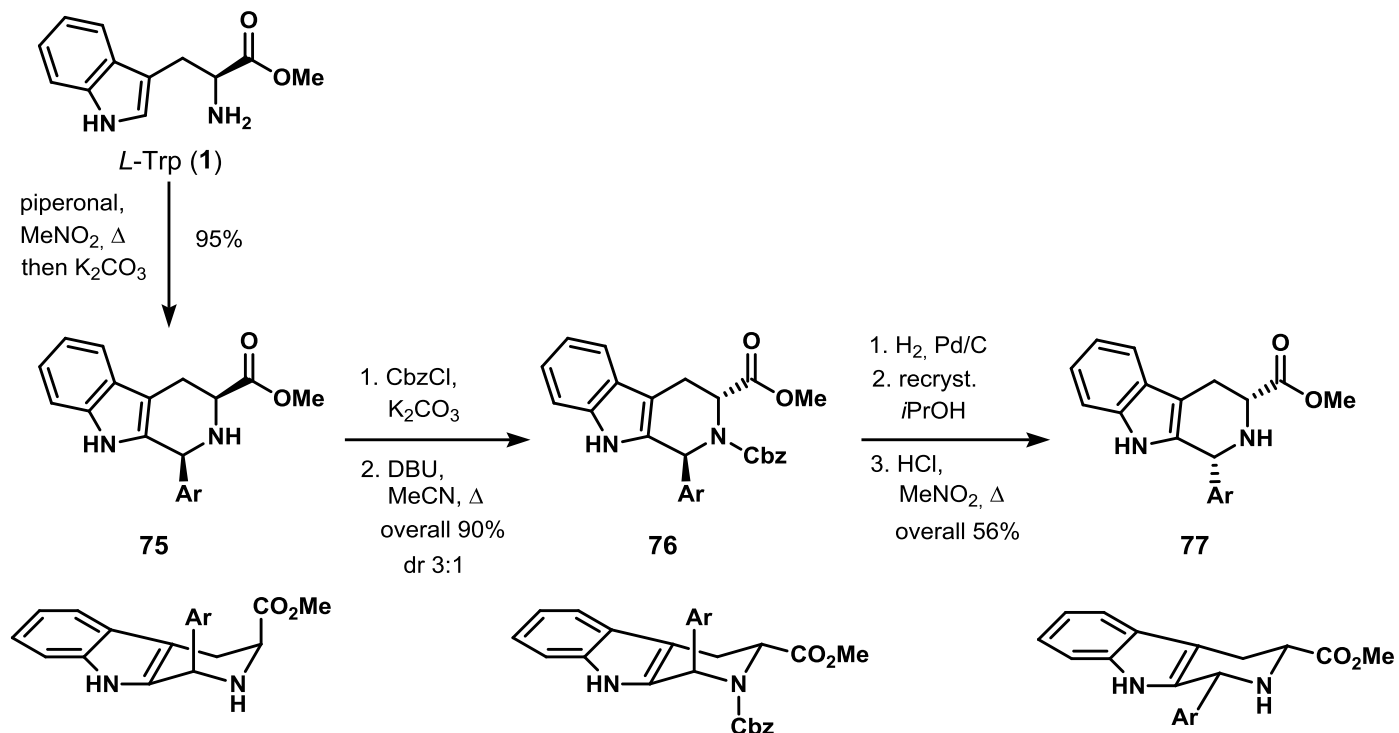
Drug synthesis

Synthesis of tadalafil out of racemic Tryptophan:[19]



Drug synthesis

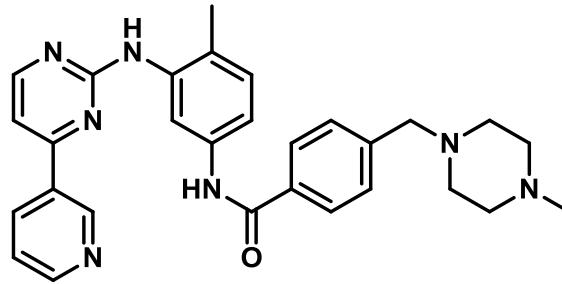
Synthesis of tadalafil out of *L*-Tryptophan methylester:^{[20],[21]}



[20] X.-X. Shi *et al. Tetrahedron Asym.* **2009**, 2090

[21] X.-X. Shi *et al. Tetrahedron Asym.* **2008**, 435

Cancer drugs



imatinib (80)

Substance name: Imatinib

Brands name: Gleevec

Company: Novartis

Medical use: Chronic myelogenous leukemia (CLM)

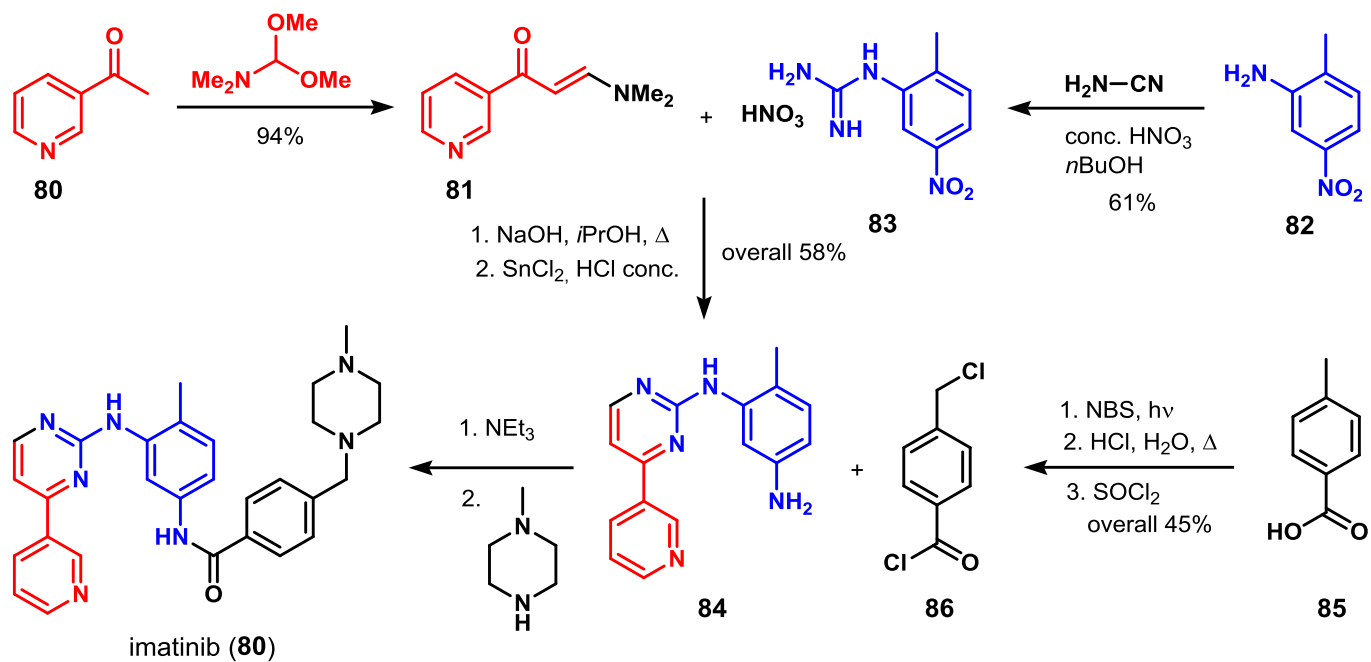
Mode of Action: Tyrosine kinase inhibitor

Rank_(Q4, 2013): 24

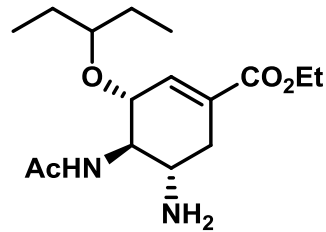
Sales_(Q4, 2013): 498 mill.US\$

Drug synthesis

Synthesis of imatinib:^[22]



AI drugs



oseltamivir (87)

Substance name: Oseltamivir

Brands name: Tamiflu

Company: Roche Pharmaceuticals

Medical use: Against influenza A and B

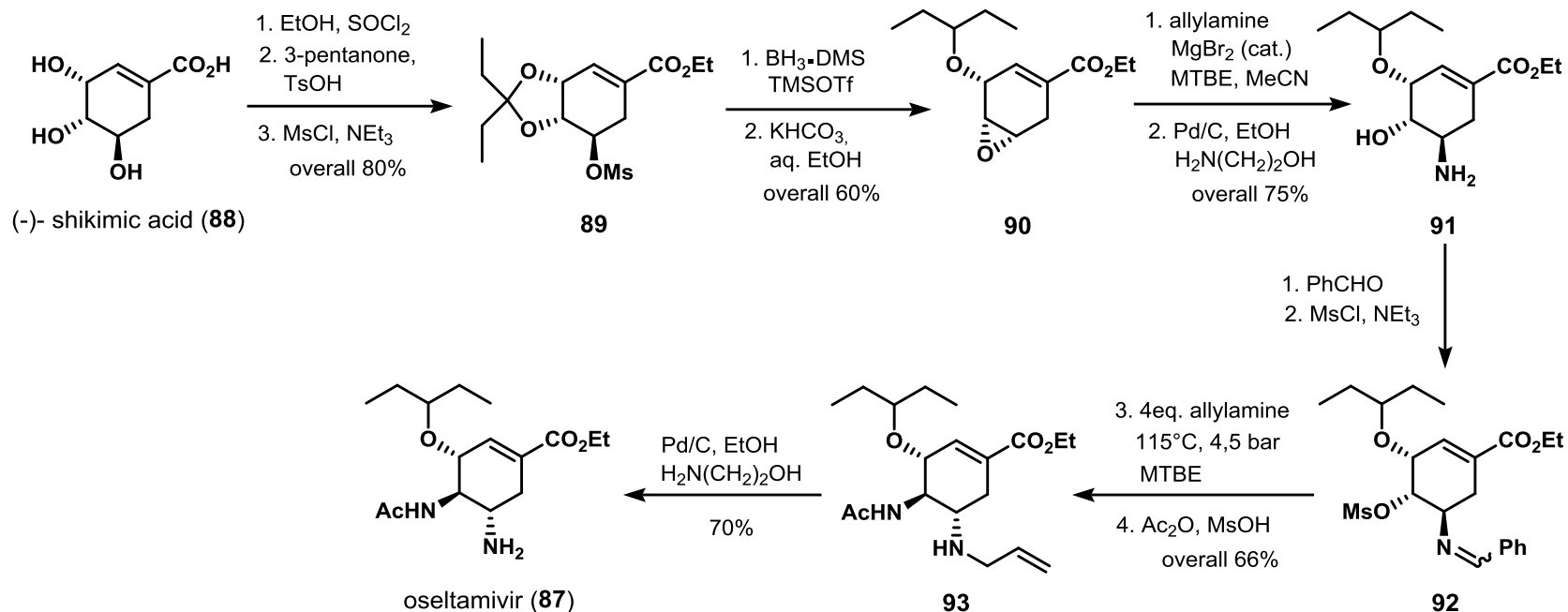
Mode of Action: Neuraminidase inhibitor

Rank_(Q4, 2013): 90

Sales_(Q4, 2013): 198 mill.US\$

Drug synthesis

Synthesis of oseltamivir:^{[23],[24],[25]}

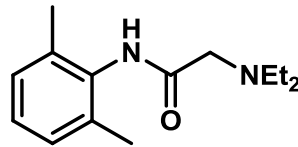


[23] J.C. Rohloff *et al.* *J. Org. Chem.* **1998**, 63, 4545

[24] M. Karpf, R. Trussardi *J. Org. Chem.* **2001**, 66, 2044

[25] other synthesis see: H. Ishikawa *et al.* *Angew. Chem. Int. Ed.* **2009**, 1304; E. J. Corey *et al.* *J. Am. Chem. Soc.* **2006**, 128, 6310

CNS drugs



lidocaine (94)

Substance name: Lidocaine

Brands name: Lidoderm

Company: Endo Pharmaceuticals

Medical use: Local anasteticum

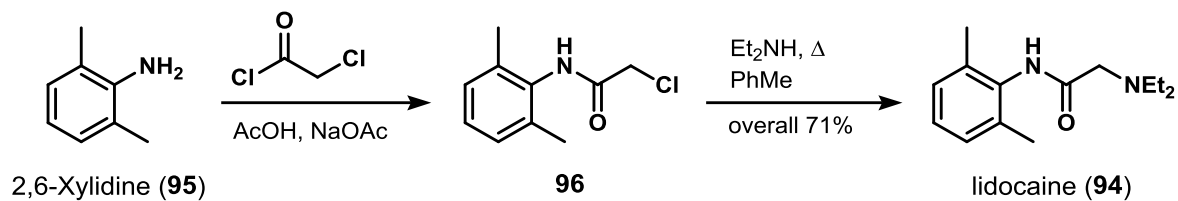
Mode of Action: Blocks the sodium channels in the neuronal cell membrane

Rank_(Q4, 2013): 71

Sales_(Q4, 2013): 226 mill.US\$

Drug synthesis

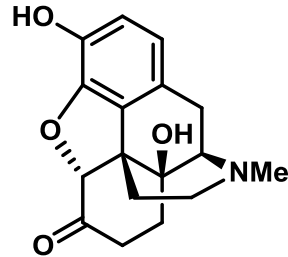
Synthesis of lidocaine:[26],[27]



[26] U.S. Patent 2441498

[27] T. J. Reilly *J. Chem. Edu.* **1999**, 76, 1557

CNS drugs



oxycodone (97)

Substance name: Oxycodone

Brands name: Oxycontin

Company: Purdue Pharma

Medical use: Against acute or chronic pain

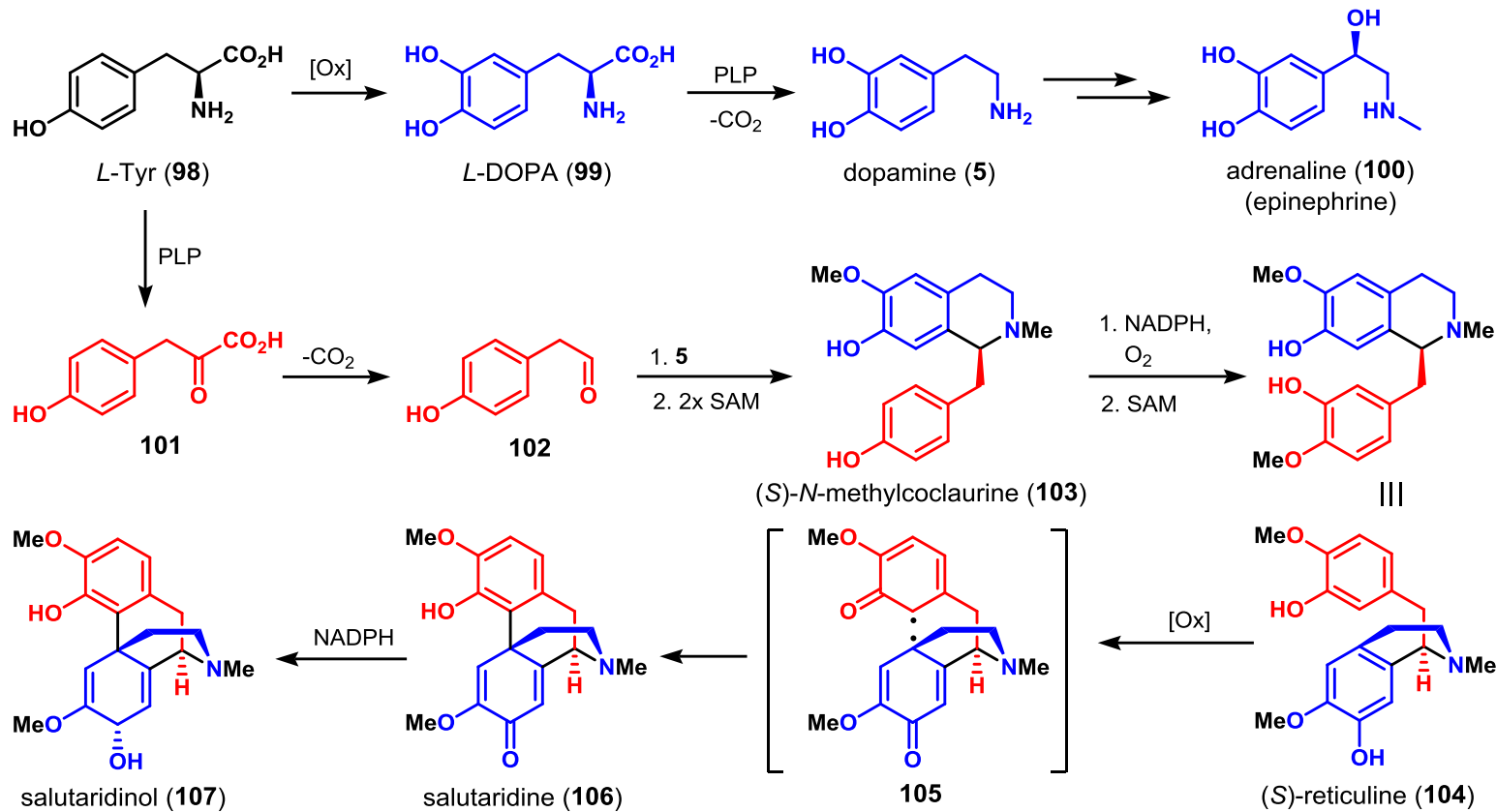
Mode of Action: Binds on opioid receptors

Rank_(Q4, 2013): 19

Sales_(Q4, 2013): 585 mill.US\$

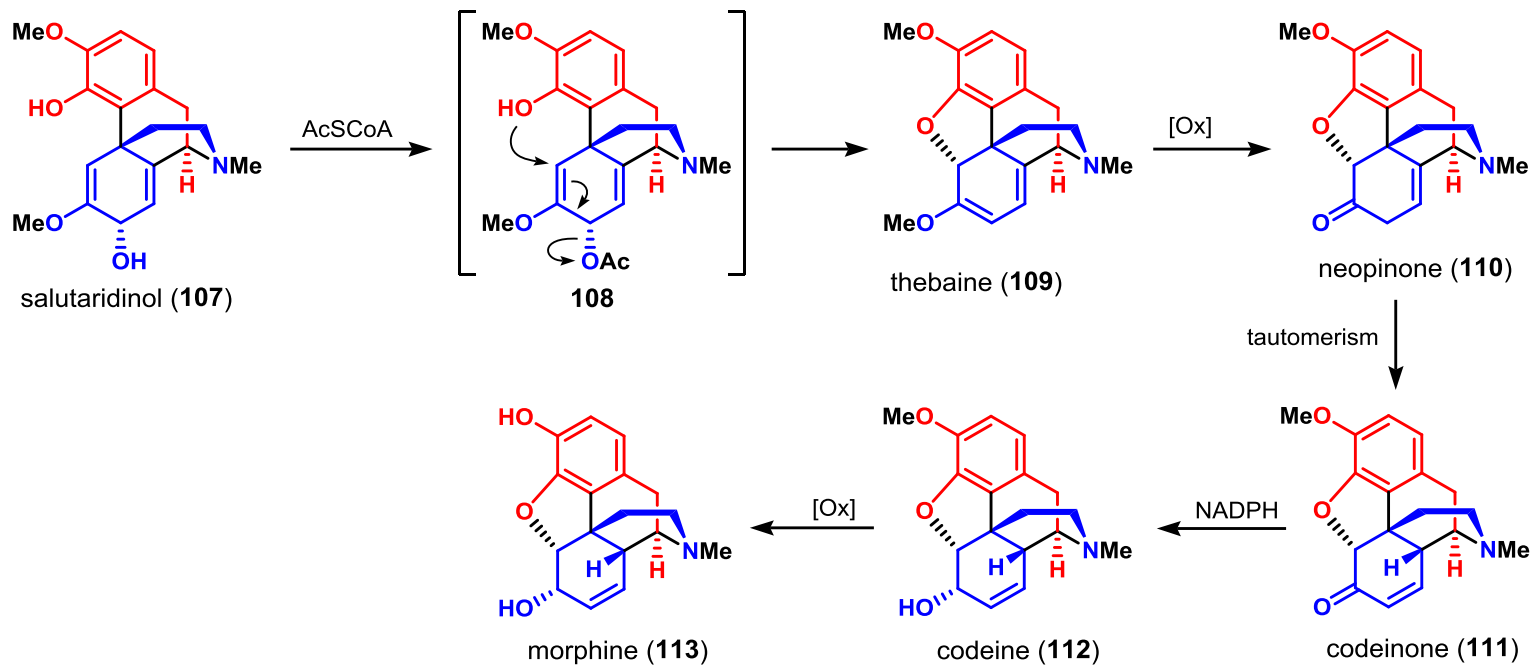
CNS drugs

Biosynthesis of morphine:



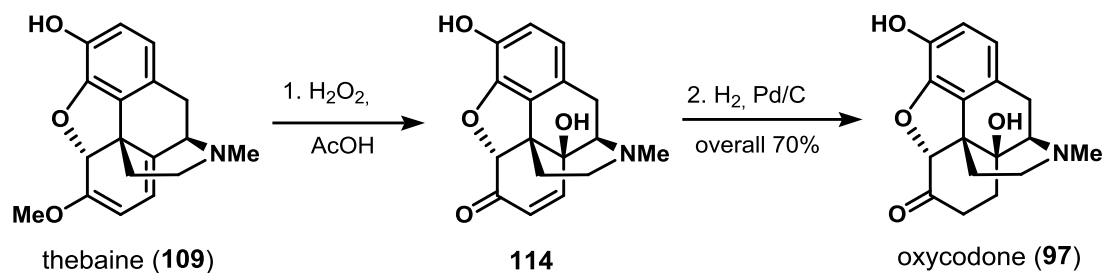
CNS drugs

Biosynthesis of morphine:



Drug synthesis

Synthesis of oxycodone:^{[28],[29]}

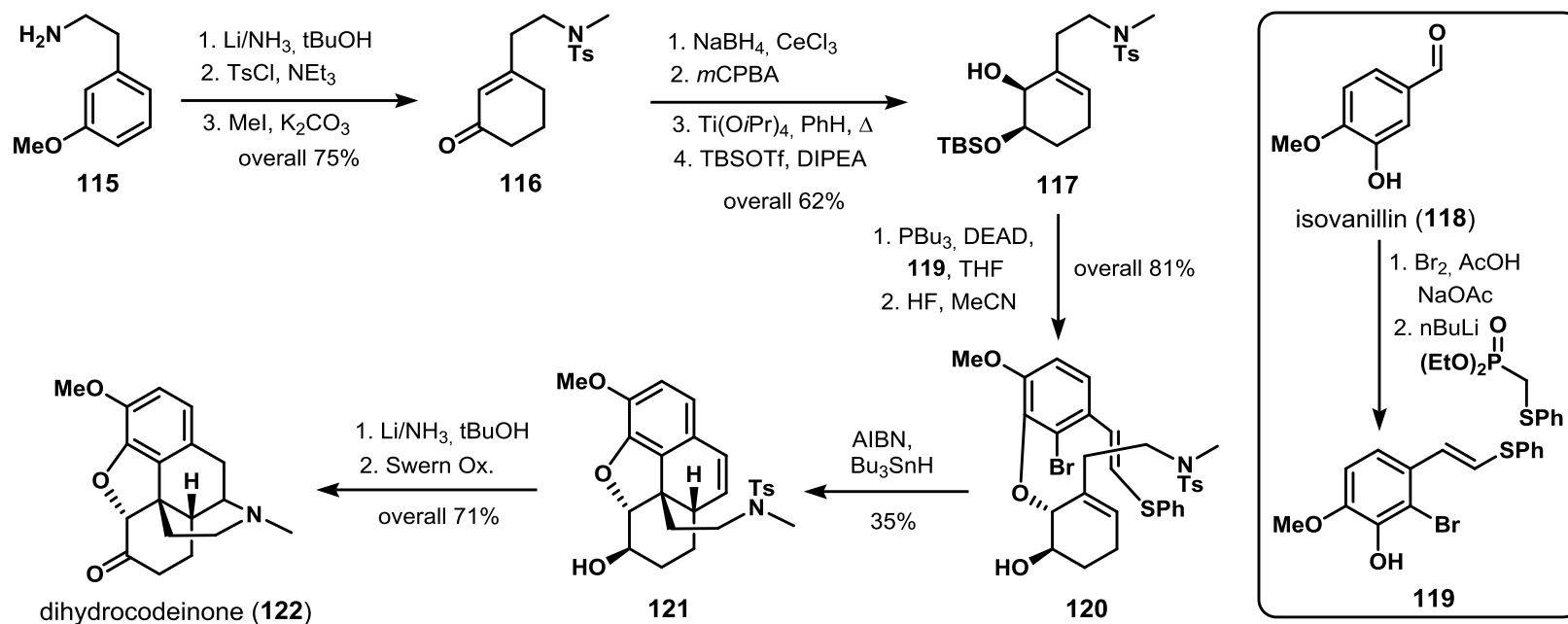


[28] US. Pat. Nos. 7,153,966 B2; 6,090,943 and 2,806,033

[29] W. Kraus Ger. Pat. 411,530 (1925)

Drug synthesis

Synthesis of morphine:^{[30],[31],[32]}



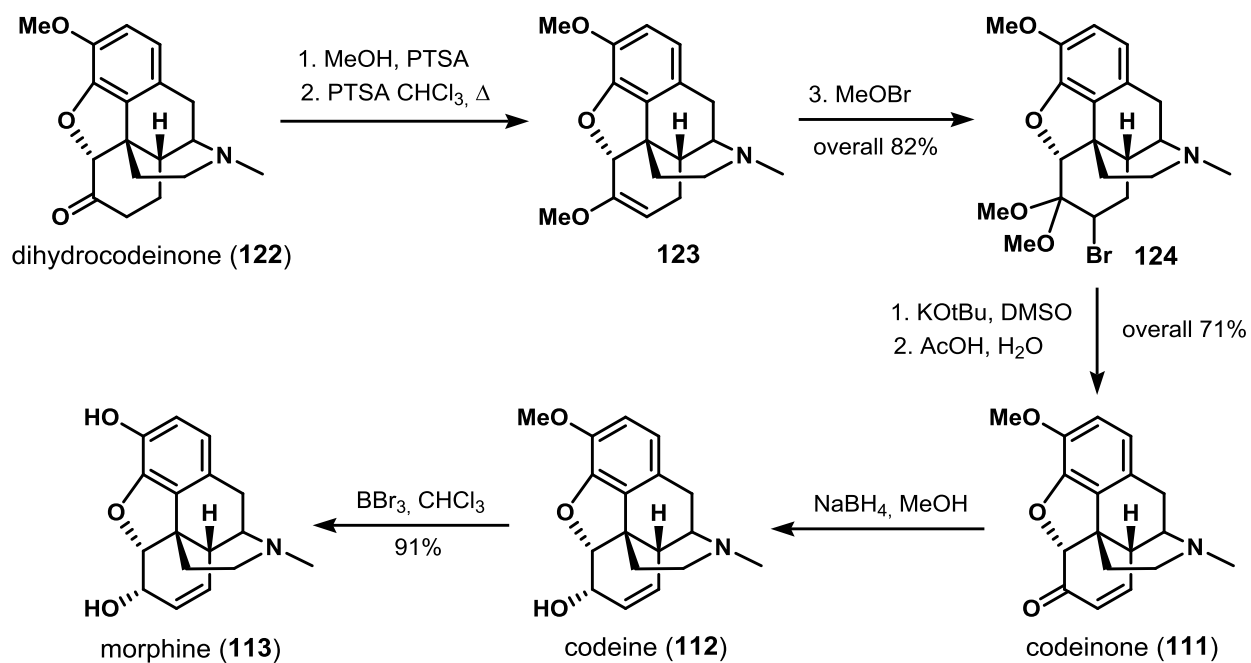
[30] K. A. Parker, D. Fokas *J. Am. Chem. Soc.* **1992**, *114*, 9688

[31] S. E. Hazlet, R. J. Brotherton *J. Org. Chem.* **1962**, *27*, 3253; E. J. Corey, J. I. Shulman *J. Org. Chem.* **1970**, *35*, 777

[32] other total syntheses see: J. Mulzer *et. al. Synlett* **1997**, 441; L. E. Overman *J. Am. Chem. Soc.* **1993**, *115*, 11028

Drug synthesis

Synthesis of morphine:^{[33],[34]}



[33] D. D. Weller, H. Rapoport *J. Med. Chem.* **1976**, *19*, 1171

[34] K. C. Rice *J. Med. Chem.* **1977**, *20*, 164; J. A. Lawson, J. I. DeGraw *J. Med. Chem.* **1977**, *20*, 165