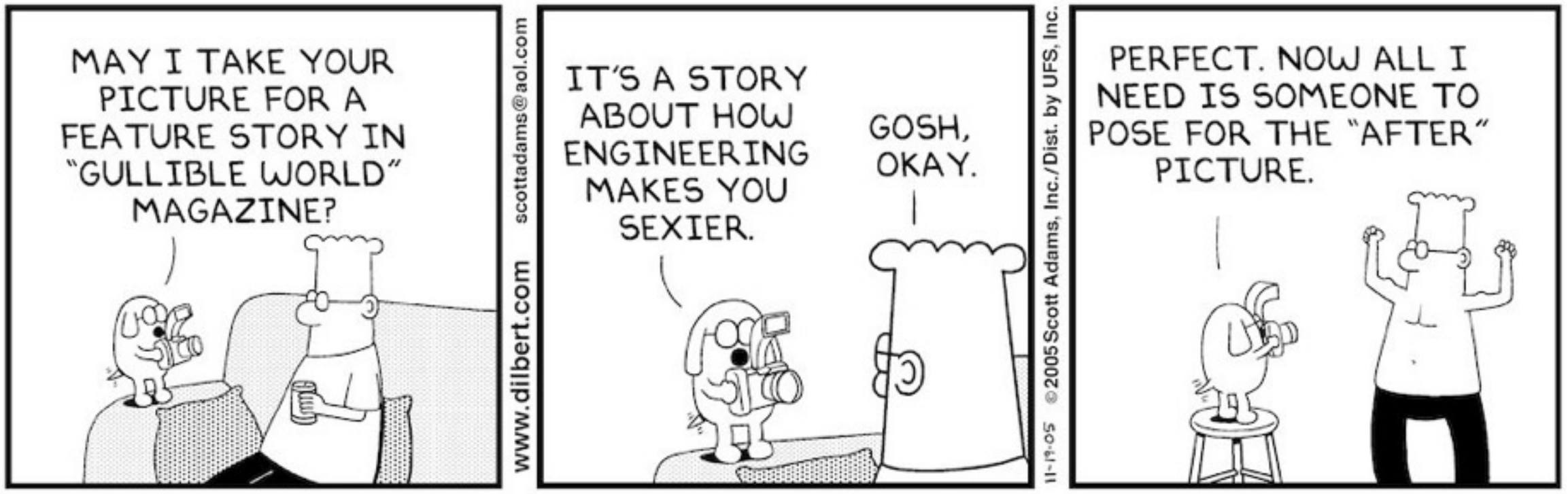
Classics in Pharmaceutical Process Chemistry



Jen Alleva, 11 December 2014

MacMillan Group Meeting

Pharmaceutical Process Research and Development

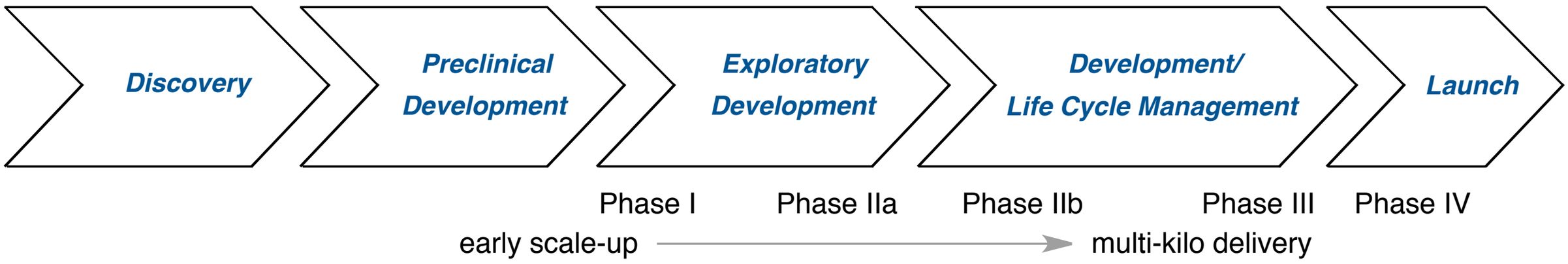
What is process chemistry?

Process Chemistry: the branch of pharmaceutical chemistry whose task is defined as the design and implementation of practical organic syntheses to support drug development and develop synthetic methods to support these process chemistry campaigns.

- design practical syntheses for and manufacturing procedures
- prepare bulk quantities of drug API to support early development
- operate within a myriad of growing regulatory requirements

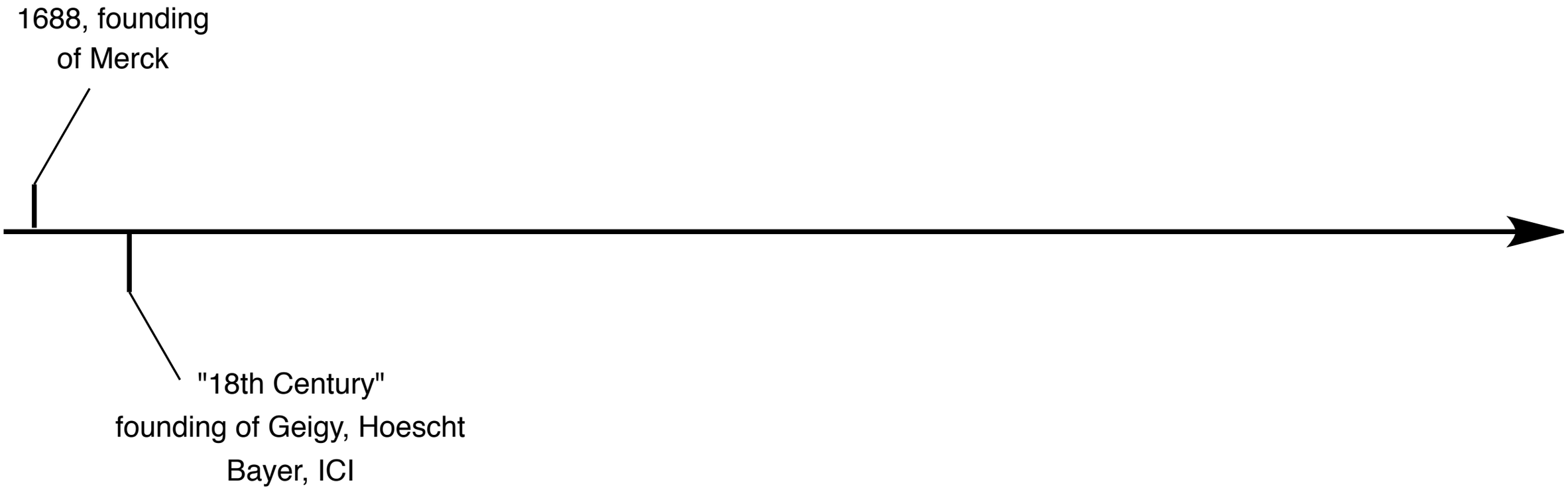
analysis of low-level impurities/parameters and kinetics, when/what process changes will be, compressed timelines

Involvement of Process R&D in Drug Development Timeline



Evolution of Pharmaceutical Process Research and Development

A Historical Perspective



Evolution of Pharmaceutical Process Research and Development

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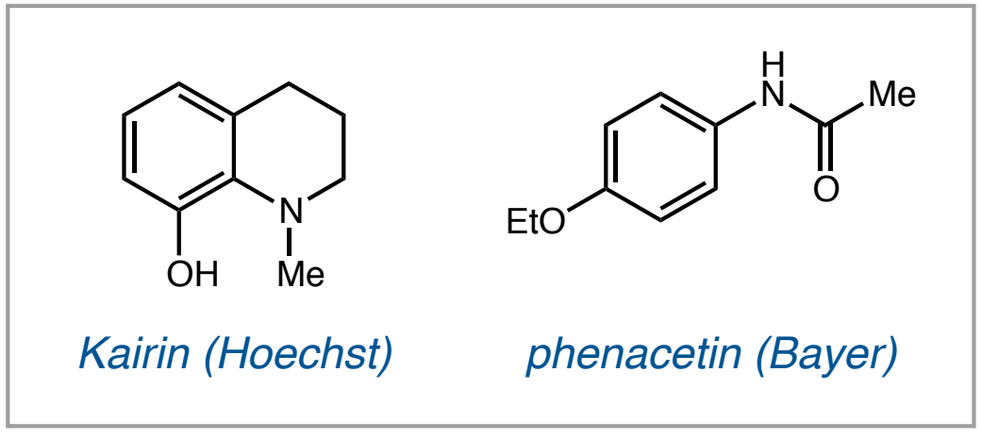
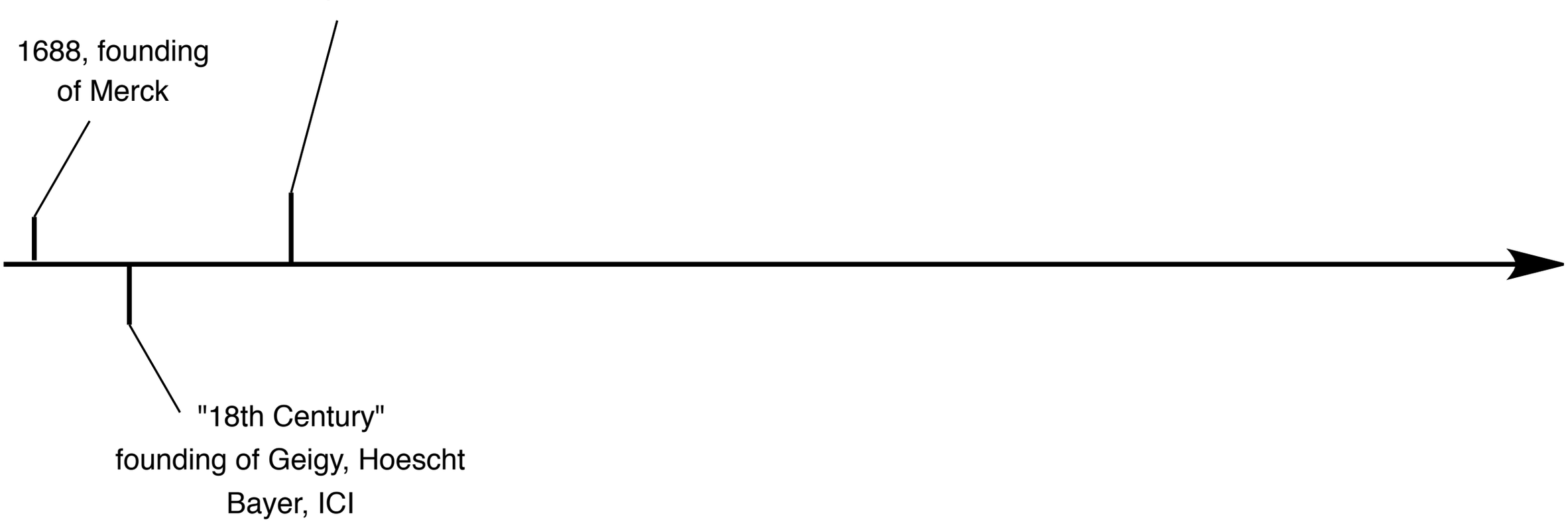


Kairin (Hoechst) *phenacetin (Bayer)*

1880's Bayer and Hoechst launch first pharmaceuticals

The birth of Process R&D

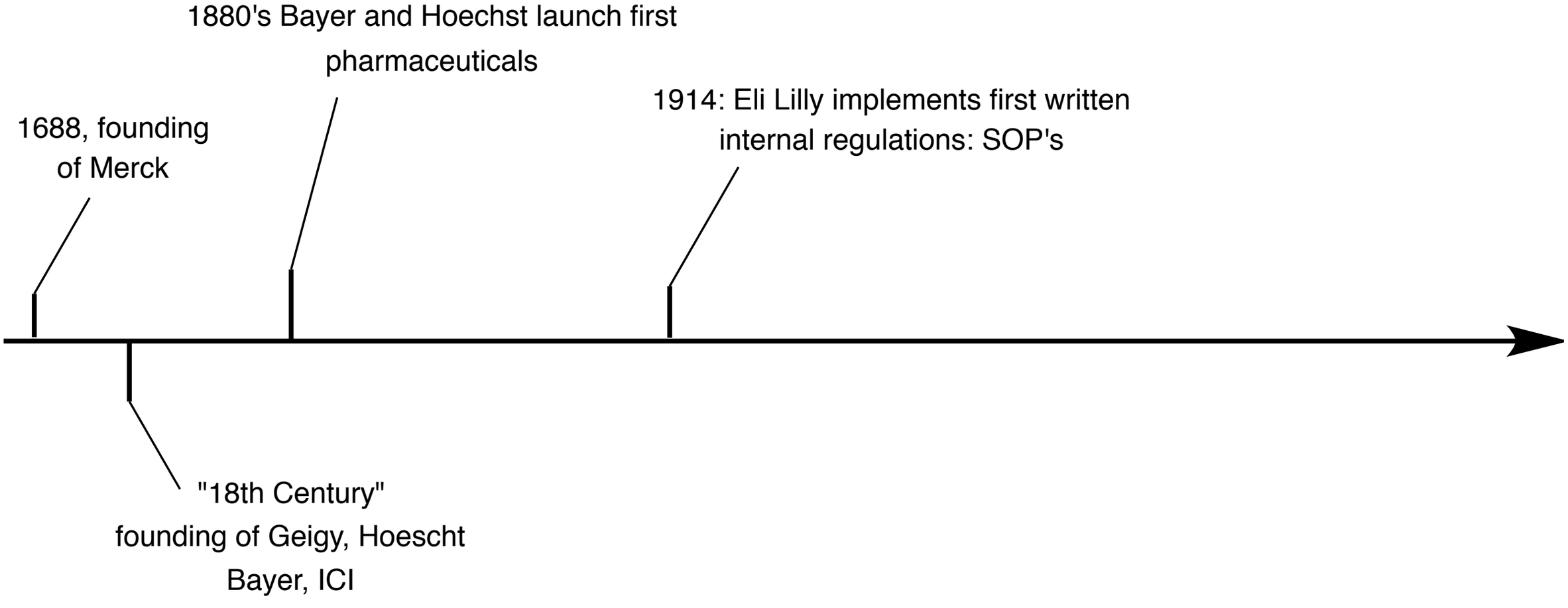
1880's Germany: Could not patent pharmaceutical products, only the process for producing them



Evolution of Pharmaceutical Process Research and Development

A Historical Perspective

" No changes in details of manufacture or packaging shall be made except by written memoranda. No written memoranda seeking to effect changes in manufacturing or packaging shall be authority for such changes unless it bears the following stamp " *Memo to Supervisors in 1914, composed by Eli Lilly*



Evolution of Pharmaceutical Process Research and Development

A Historical Perspective

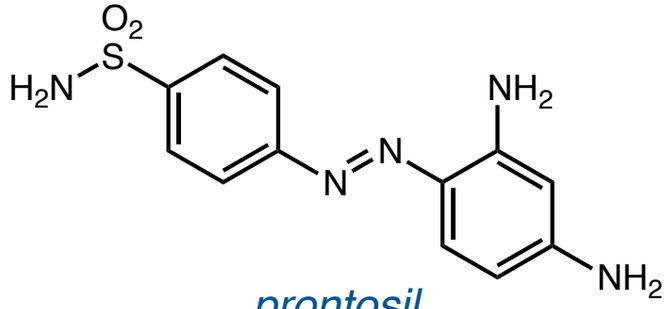
1880's Bayer and Hoechst launch first pharmaceuticals

1688, founding of Merck

1914: Eli Lilly implements first written internal regulations: SOP's

"18th Century" founding of Geigy, Hoescht Bayer, ICI

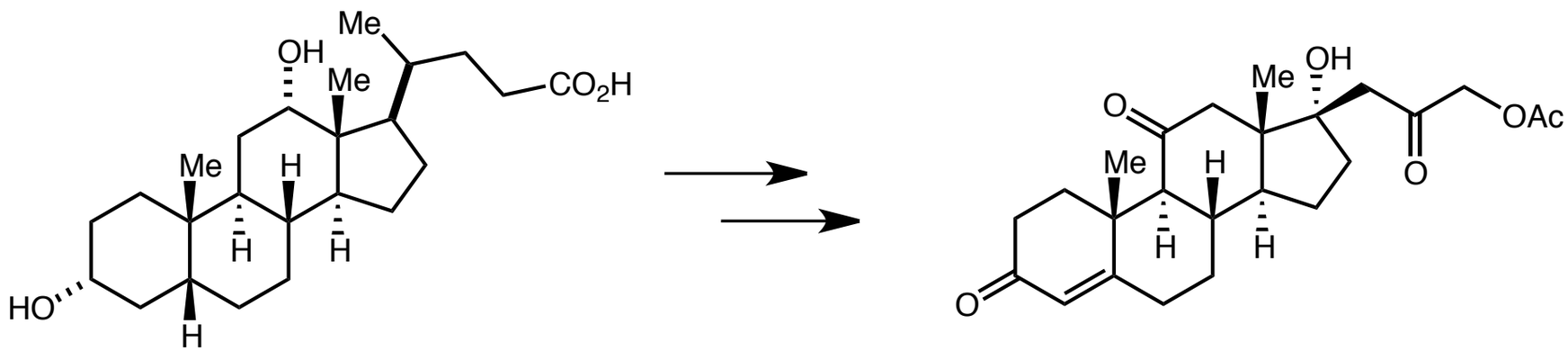
1932: Bayer launches first commercial antibiotic



prontosil

Evolution of Pharmaceutical Process Research and Development

A Historical Perspective



Desoxycholic acid → *Cortisone*

1880's Bayer and Hoechst launch first pharmaceuticals

1688, founding of Merck

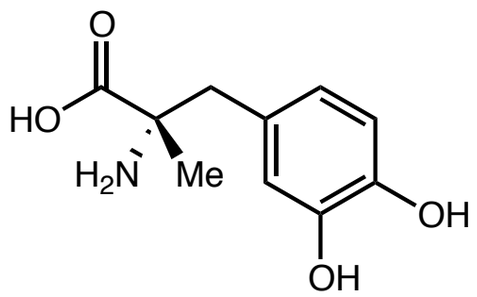
"18th Century" founding of Geigy, Hoescht Bayer, ICI

1914: Eli Lilly implements first written internal regulations: SOP's

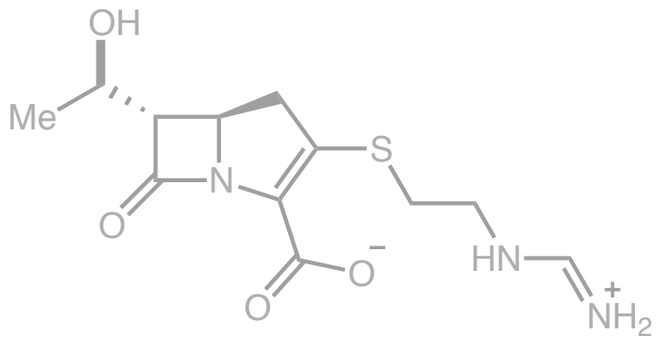
1932: Bayer launches first commercial antibiotic

1950–1953: Merck's synthesis of Cortisone

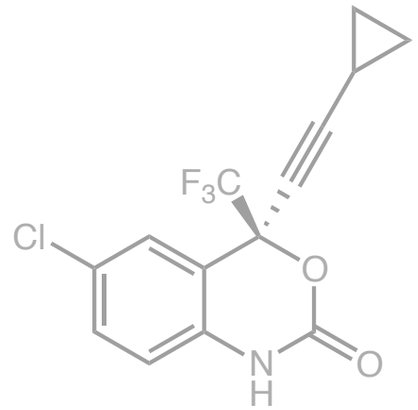
Classic Syntheses in Pharmaceutical Process Research and Development



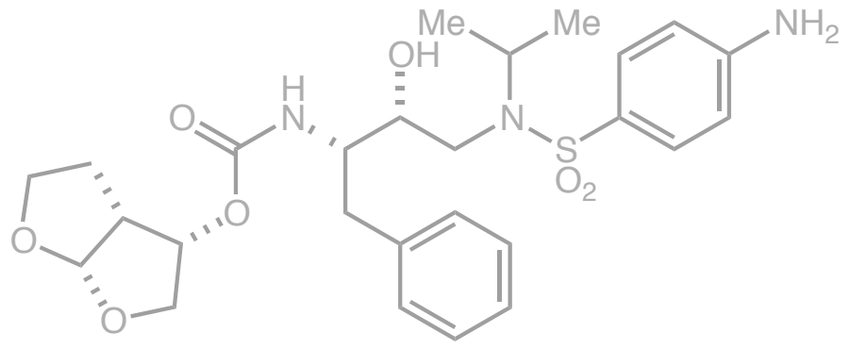
Methyldopa



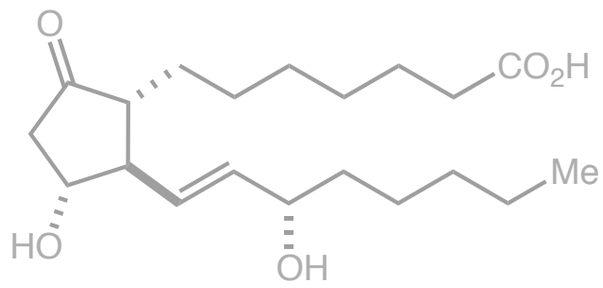
Imipenem



Efavirenz

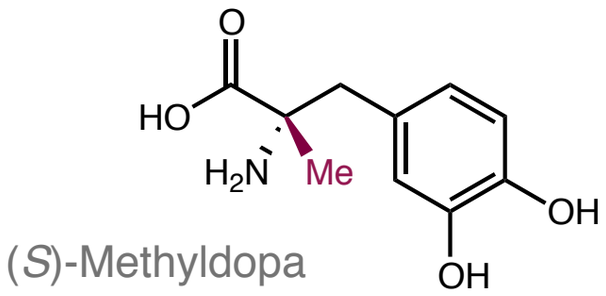


Darunavir



Prostaglandin E_1

The Merck Synthesis of L-Methyldopa



(*S*)-Methyldopa

- selective α-adrenergic receptor agonist
- psychoactive drug used to treat hypertension
- WHO list of essential medications
- safe for gestational hypertension

"Give 'em L boys!"

- Max Tishler, president of Merck & Co.

Key Features of Merck's Synthesis

utilization of a continuous flow system established to resolve enantiomers

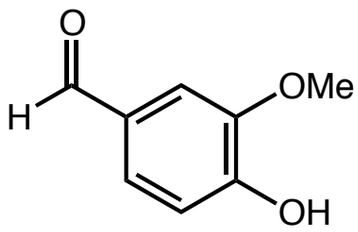
best in overall atom economy

still in use today despite major advances in asymmetric catalysis

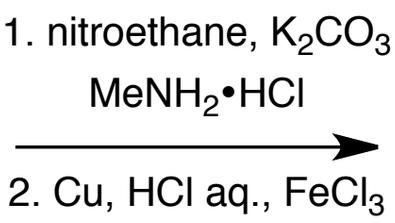
Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

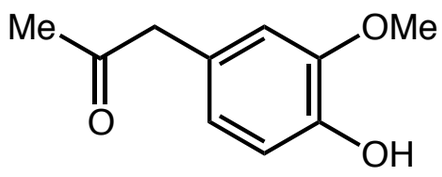
The Merck Synthesis of L-Methyldopa

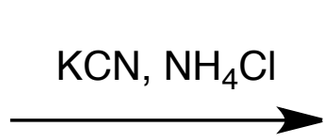
Merck & Co.'s Process and Manufacturing Route to Methyldopa

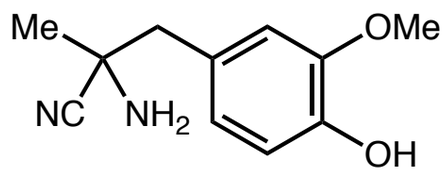


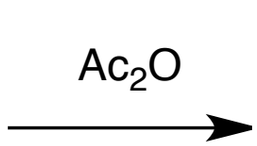
vanillin

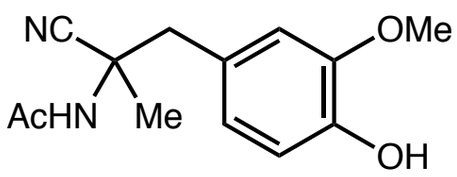


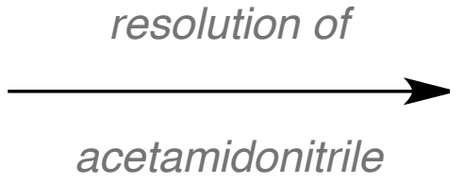


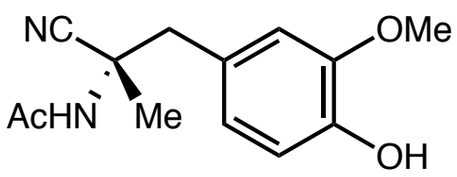


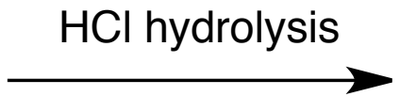


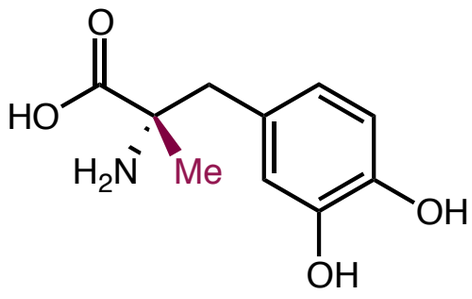










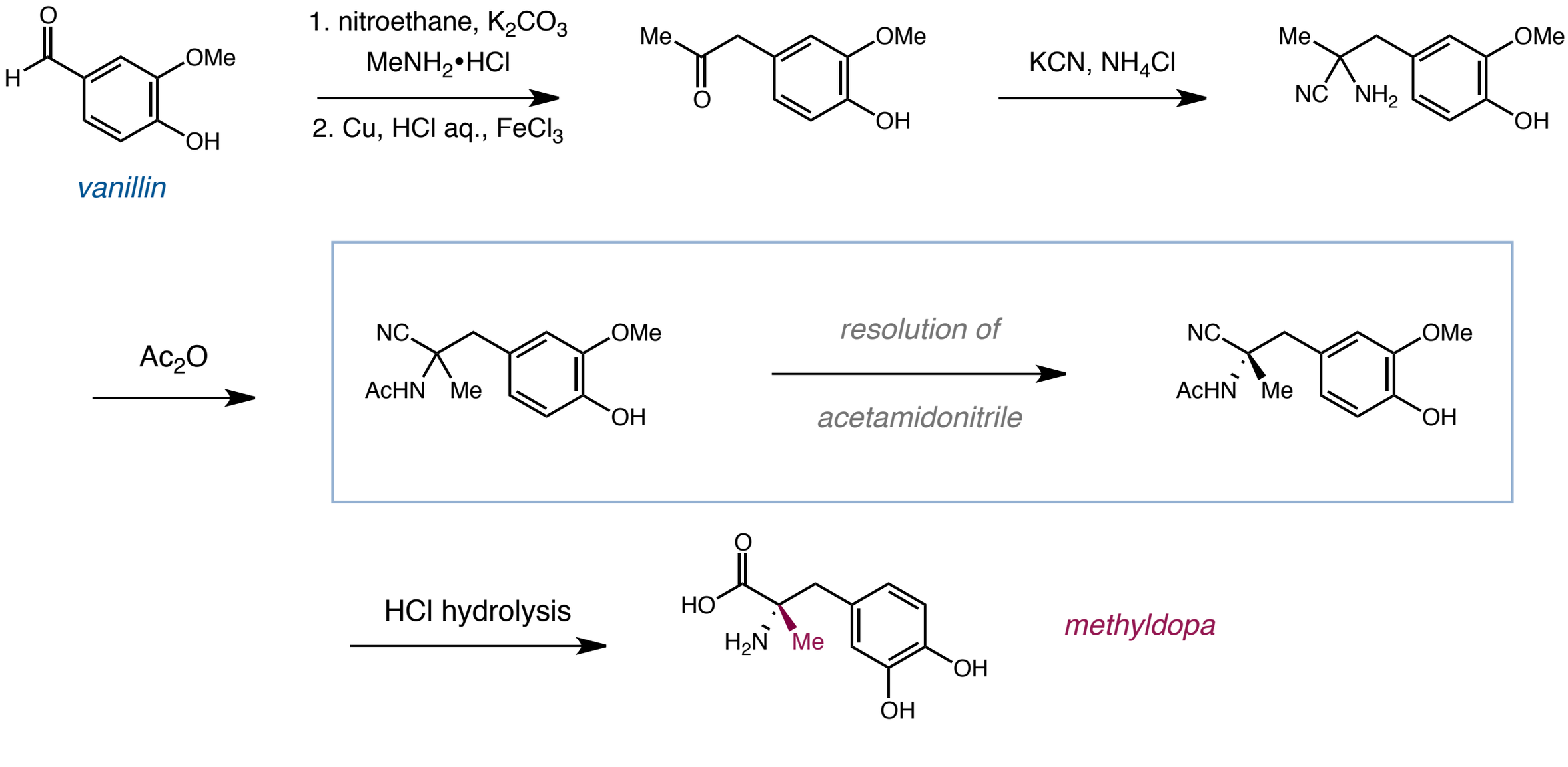


methyldopa

Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

The Merck Synthesis of L-Methyldopa

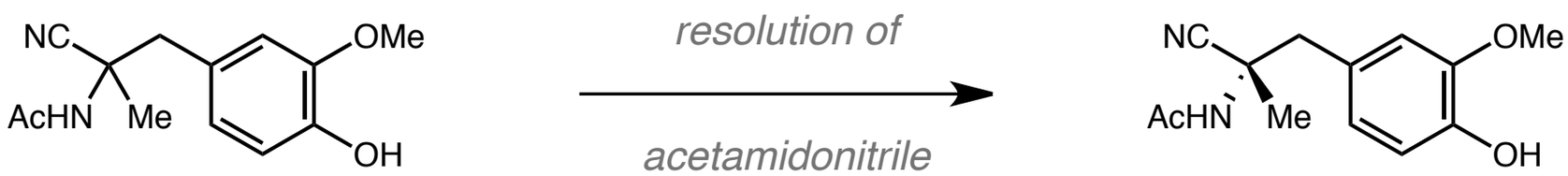
Merck & Co.'s Process and Manufacturing Route to Methyldopa



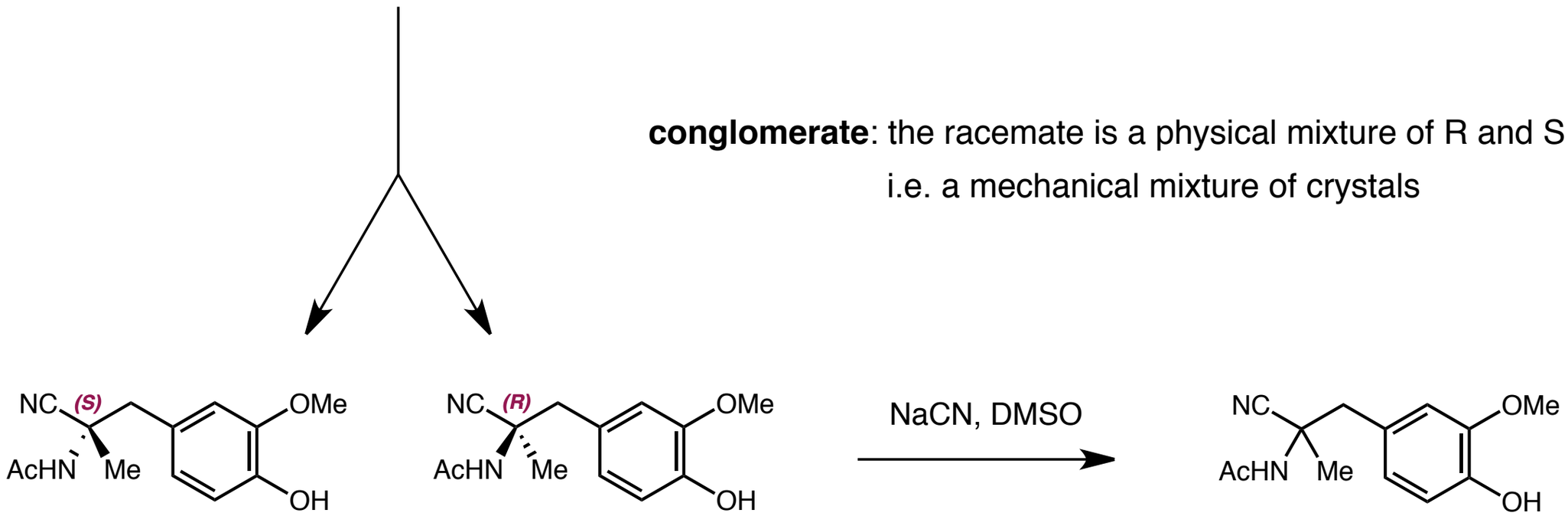
Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

The Merck Synthesis of L-Methyldopa

Continuous Flow Resolution Provides both Enantiomers of Methyldopa



conglomerate: the racemate is a physical mixture of R and S forms
i.e. a mechanical mixture of crystals



desired

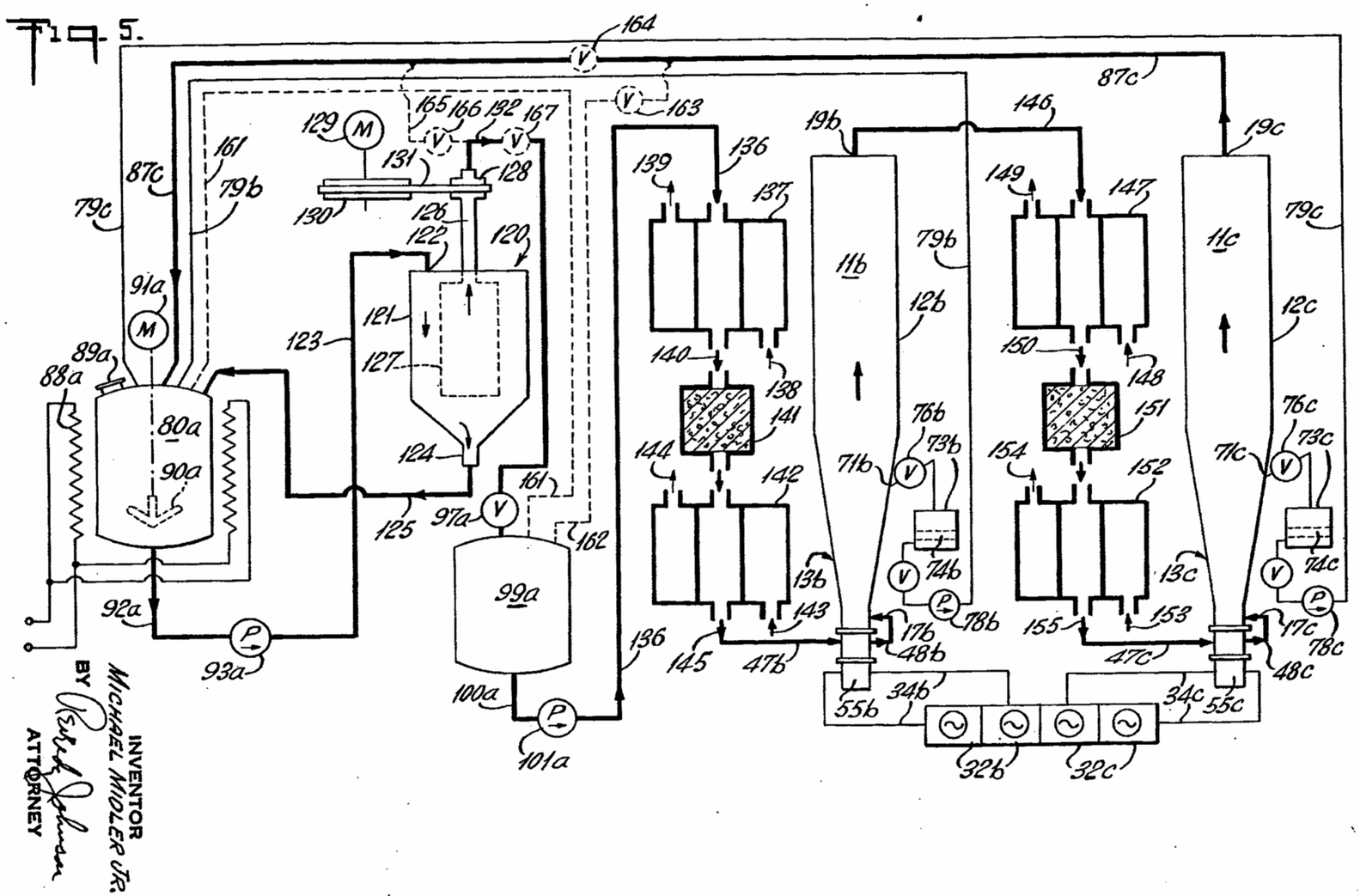
resubjected to resolution

A seeded, supersaturated solution of one enantiomer allows for selective crystallization of desired product

Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

The Merck Synthesis of L-Methyldopa

Continuous Flow Resolution Provides both Enantiomers of Methyldopa

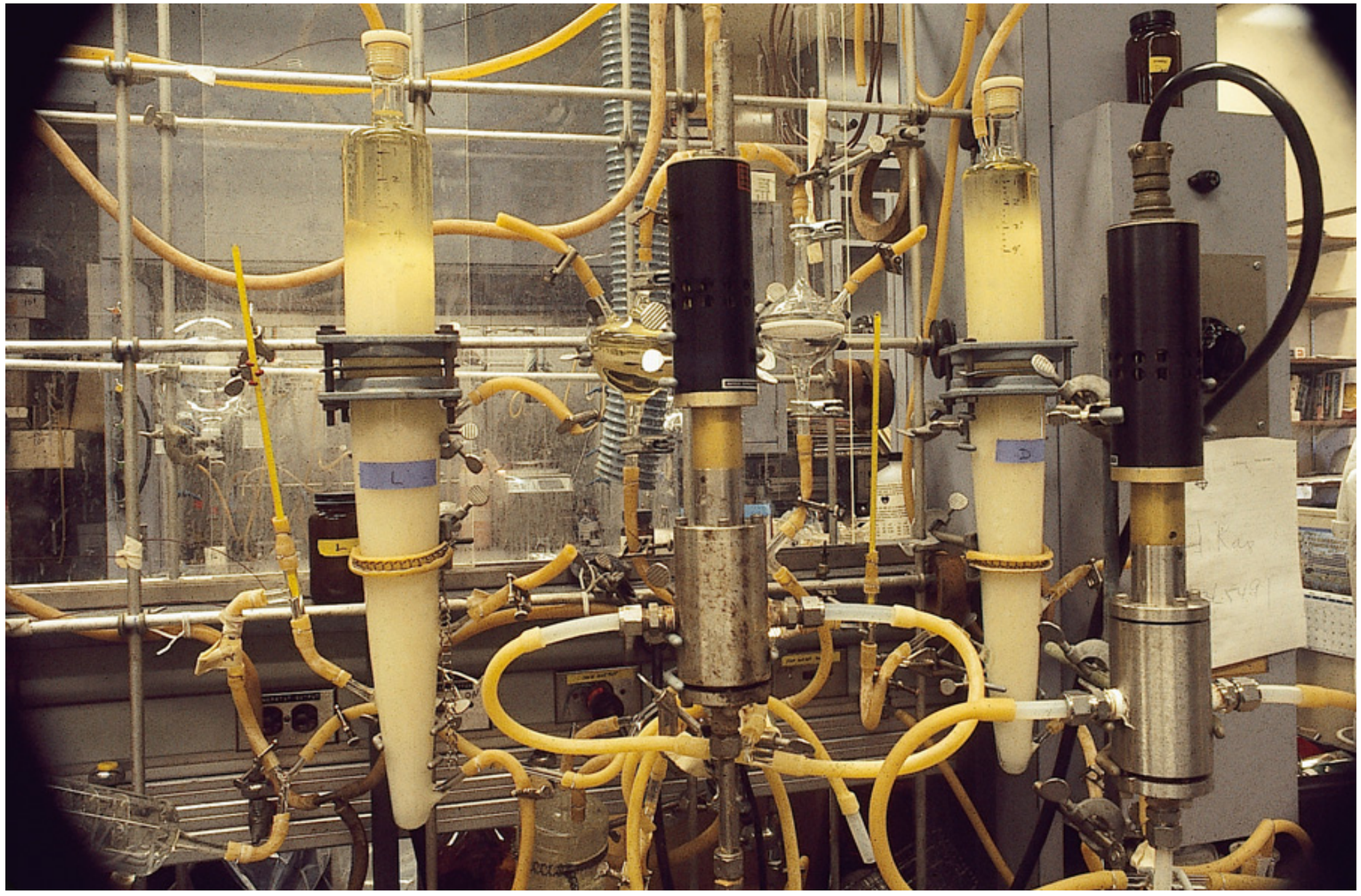


Paul Reider

Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

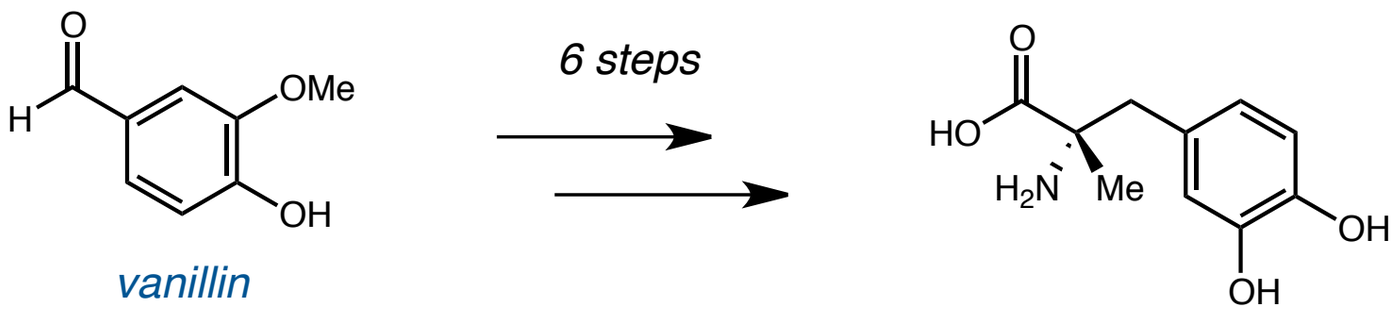
The Merck Synthesis of L-Methyldopa

Continuous Flow Resolution Provides both Enantiomers of Methyldopa



Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

The Merck Synthesis of L-Methyldopa

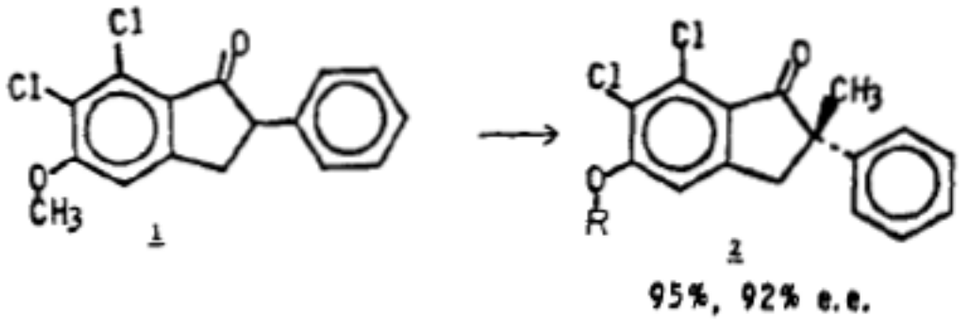


vanillin *methyldopa*

practical synthesis still in use today for the manufacture of Methyldopa

Merck's asymmetric alkylation via PTC:

Scheme I

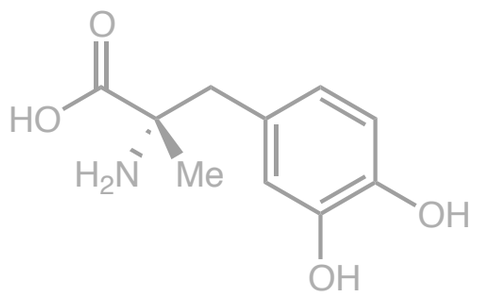


despite recent advances in asymmetric catalysis, continuous resolution continues to be most robust and cost effective method of preparation

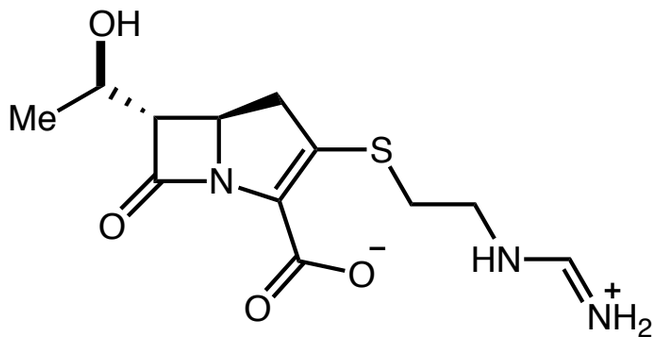
Dolling, U.-H.; David, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.,* **1984**, *106*, 446

Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

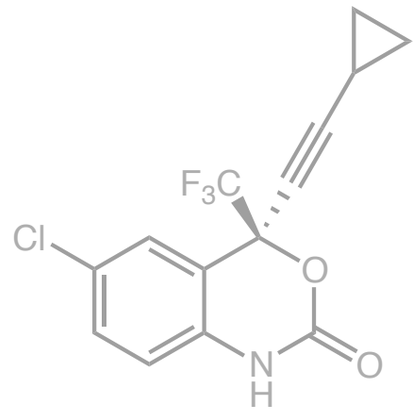
Classic Syntheses in Pharmaceutical Process Research and Development



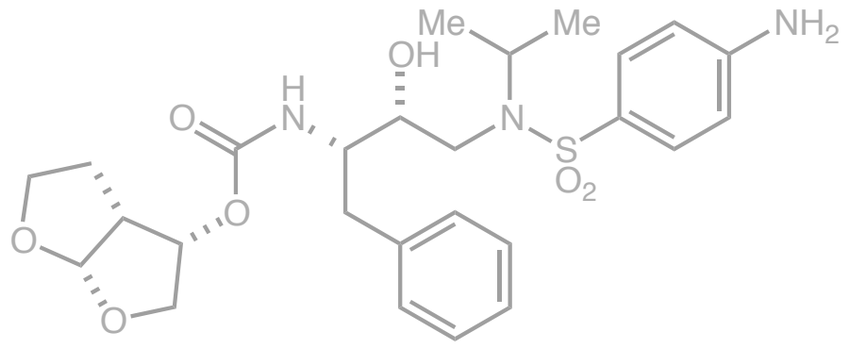
Methyldopa



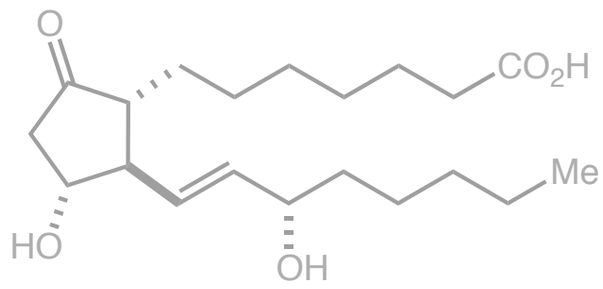
Imipenem



Efavirenz



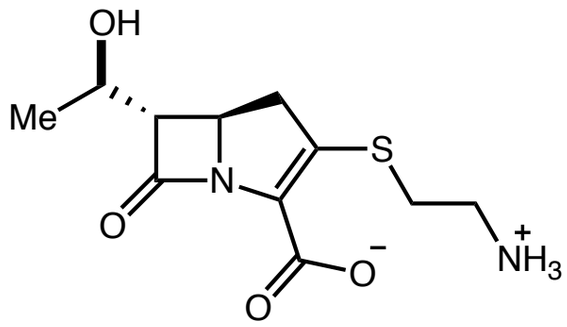
Darunavir



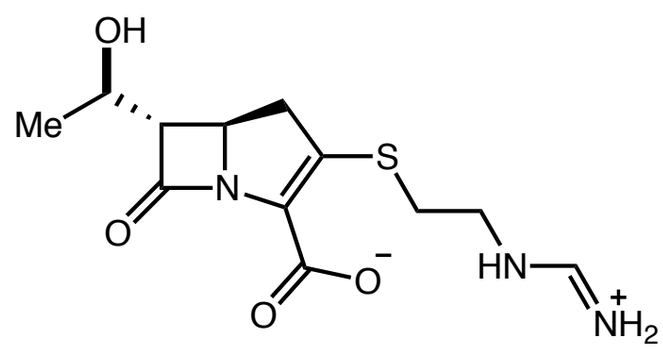
Prostaglandin E_1

The Merck Synthesis of Imipenem

The First Carbapenem Antibiotic



Thienamycin



Imipenem

NJ Pine Barrens: Apple Pie Hill

- first carbapenem and carbapenem antibiotic
- Fermentation ultimately a failure (~100mg/kg)
- 2nd order reaction of thienamycin with itself
- multiple total syntheses by Merck process

"To produce 40,000kg of imipenem per year, we would have to run the thienamycin fermentation in Lake Erie and pump to Lake Ontario for workup." - Ed Paul

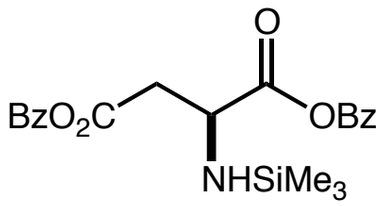
photo: Farmartin:en.wikipedia

Grabowski, E. J. J. *ACS Symposium Series*, **2004**, 870 (Chemical Process Research)

Grabowski, E. J. J. *Chirality*, **2005**, *17*, S249

The Merck Synthesis of Imipenem

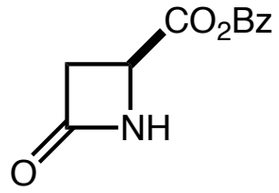
Merck's First Generation Process Synthesis



protected L-aspartic acid

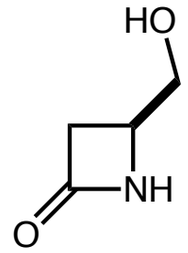
tBuMgCl, Et_2O, 0°C

2N, HCl, NH_4Cl



$NaBH_4$

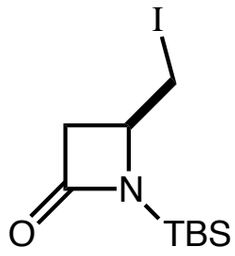
MeOH



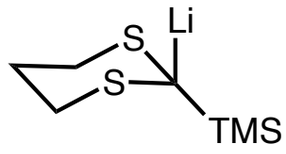
1. MsCl, NEt_3, CH_2Cl_2, 0 °C

2. NaI, acetone, Δ

3. TBSCl, NEt_3, DMF



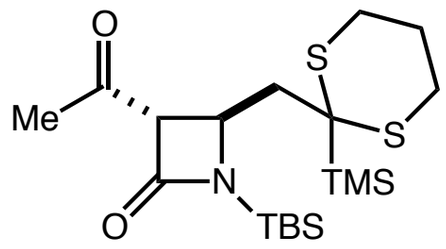
50% overall yield



1. THF, –78 °C, 80%

2. acetaldehyde, LDA, THF, –78 °C

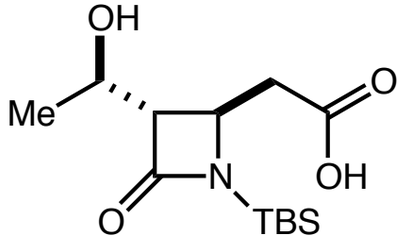
3. TFAA, DMSO, NEt_3, CH_2Cl_2 –78 °C



1. K-Selectride, KI, Et_2O, 87%

2. $HgCl_2$, HgO, MeOH aq., Δ

3. H_2O_2, MeOH aq. , 76%

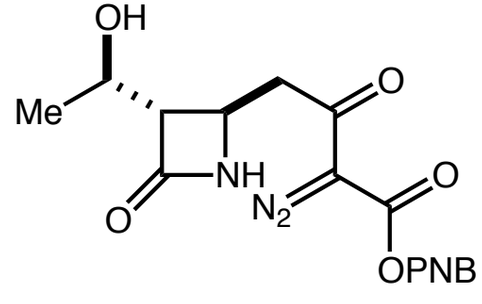


1. CDI, THF

2. $MgO_2CCH_2CO_2PNB$, THF

3. HCl, MeOH

4. $PhSO_2N_3$, Et_3N, MeCN

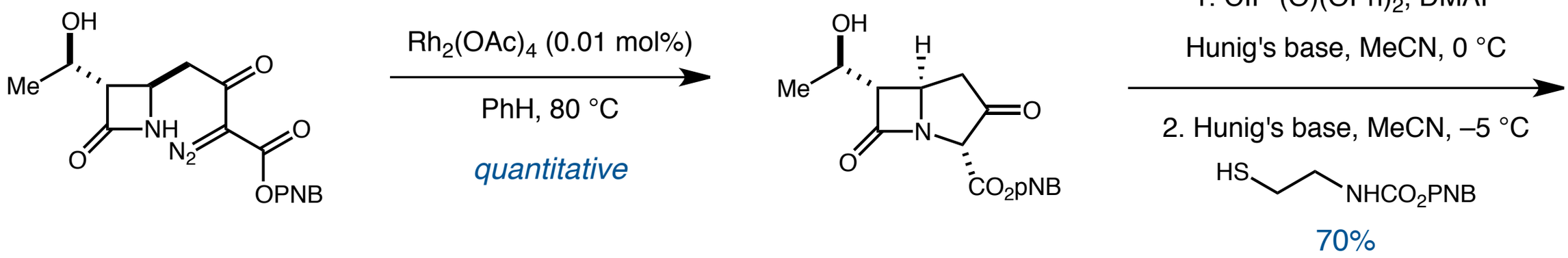


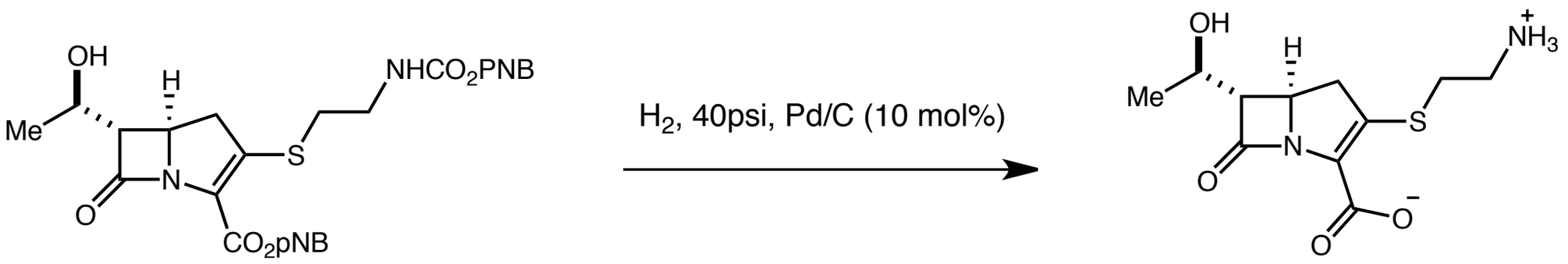
90%

Karady, S.; Amato, J.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.,* **1980**, *103*, 6765

The Merck Synthesis of Imipenem

Merck's First Generation Process Synthesis





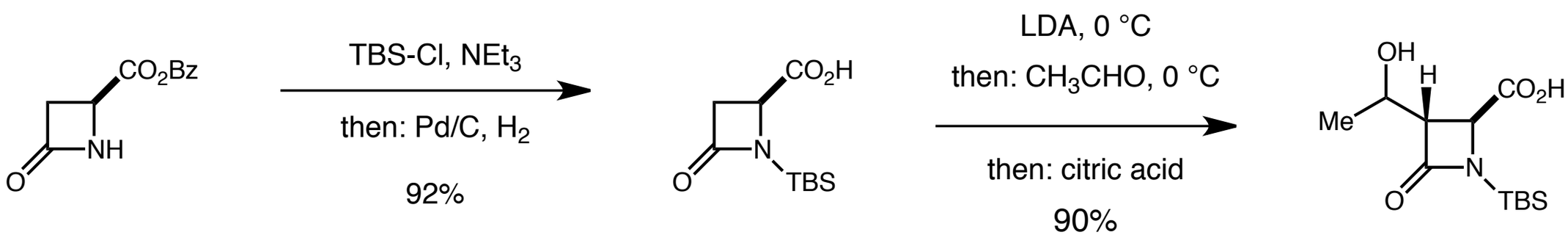
thienamycin

19 chemical steps

Karady, S.; Amato, J.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.,* **1980**, *103*, 6765

The Merck Synthesis of Imipenem

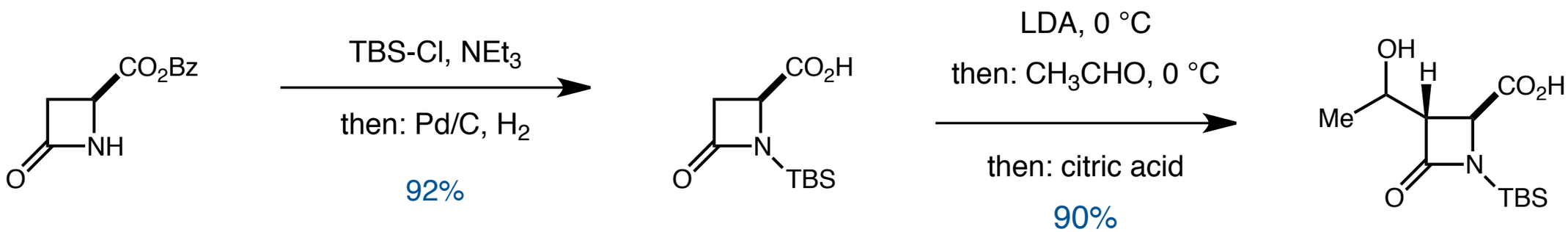
Merck's Second Generation Process Synthesis: Current Manufacturing Route



Reider, P. J.; Grabowski, E. J. J. *Tet. Lett.,* **1982**, *23*, 2293

The Merck Synthesis of Imipenem

Merck's Second Generation Process Synthesis: Current Manufacturing Route



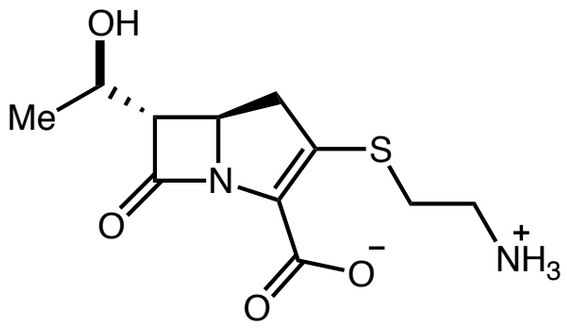
thienamycin

10 chemical steps

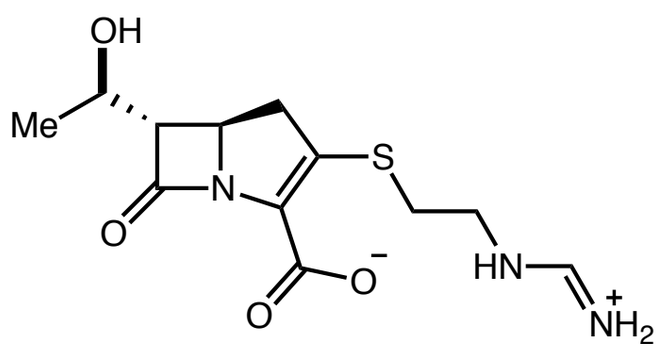
Reider, P. J.; Grabowski, E. J. J. *Tet. Lett.,* **1982**, *23*, 2293

The Merck Synthesis of Imipenem

The First Carbapenem Antibiotic



Thienamycin



Imipenem

first carbapenem natural product antibiotic to make it to market

6+ syntheses of Thienamycin reported in this era

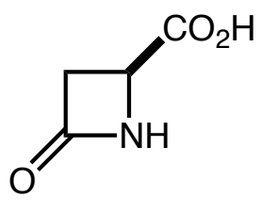
Reider's publication received over 100 citations in the first year

Total synthesis on-scale

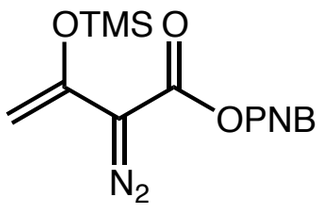
on-scale synthesis using Rh catalyzed transformation

early syntheses utilized Mitsunobu reaction

to set alcohol stereocenter



Karady's synthesis

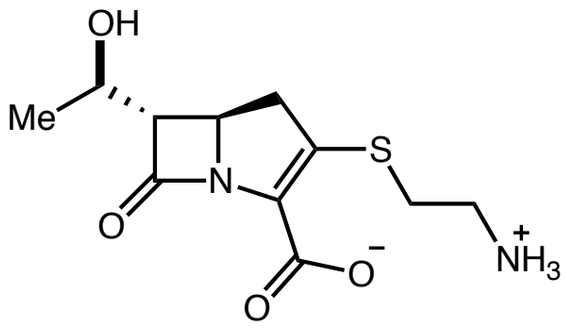


from Penicillin synthesis

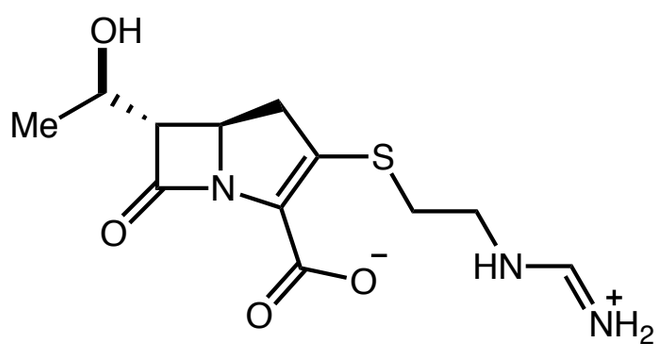
Grabowski, E. J. J. *ACS Symposium Series*, **2004**, 870 (Chemical Process Research)

The Merck Synthesis of Imipenem

The First Carbapenem Antibiotic



Thienamycin



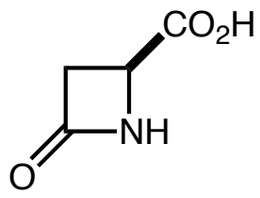
Imipenem

first carbapenem natural product antibiotic to make it to market

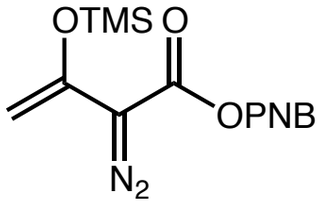
6+ syntheses of Thienamycin reported in this era

Reider's publication received over 100 citations in the first year

"Frankenstein" synthesis highlights level of collaboration and creativity of Merck's process chemistry group



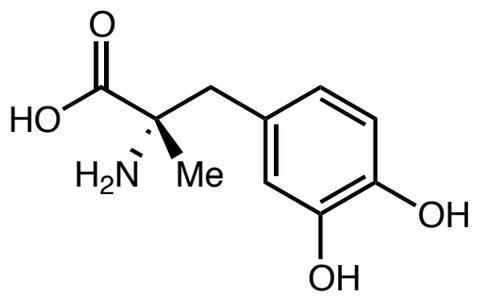
Karady's synthesis



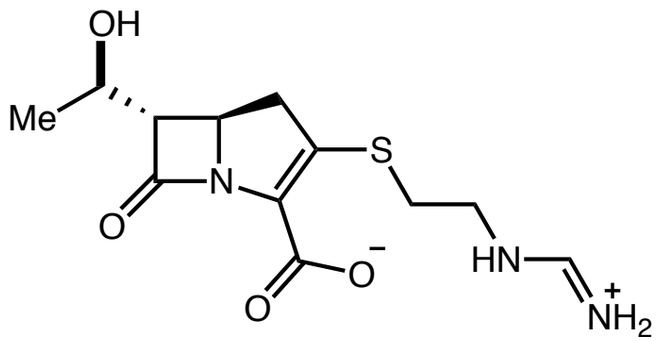
from Penicillin synthesis

Grabowski, E. J. J. *ACS Symposium Series*, **2004**, 870 (Chemical Process Research)

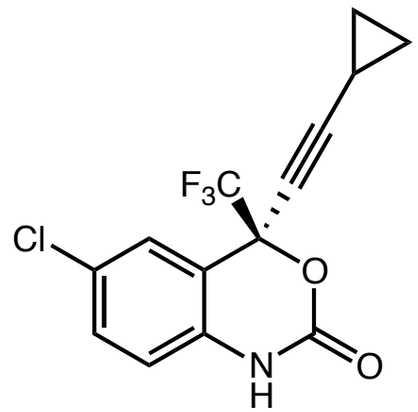
Classic Syntheses in Pharmaceutical Process Research and Development



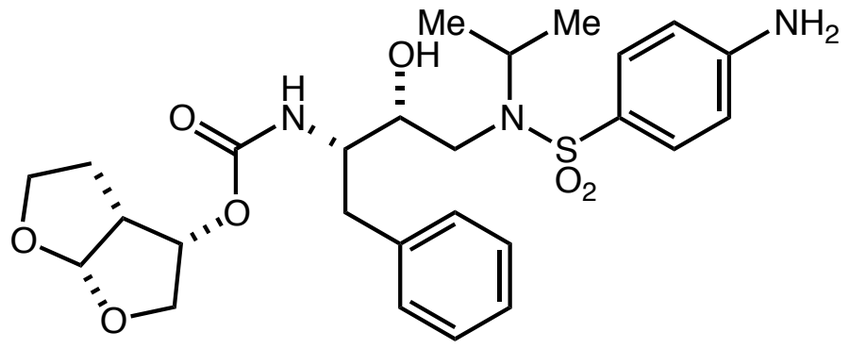
Methyldopa



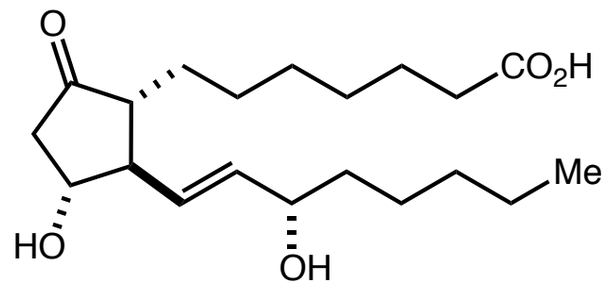
Imipenem



Efavirenz

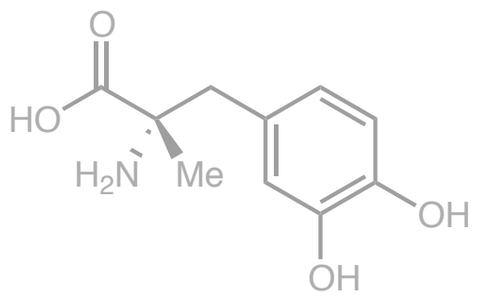


Darunavir

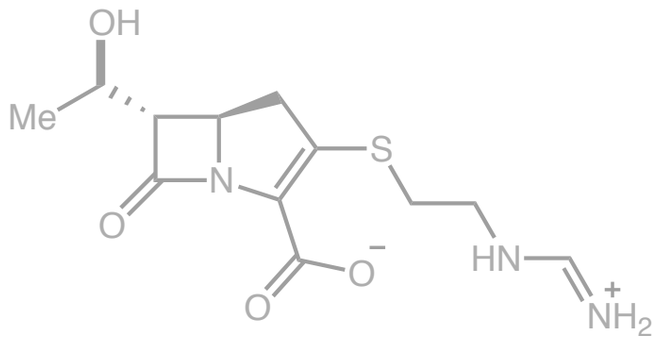


Prostaglandin E_1

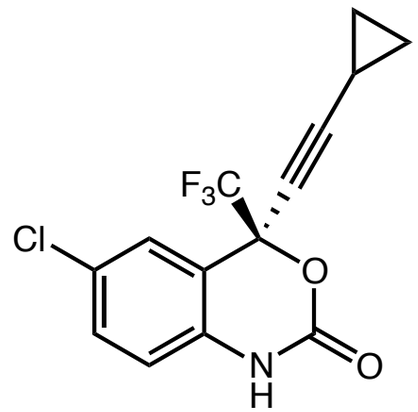
Classic Syntheses in Pharmaceutical Process Research and Development



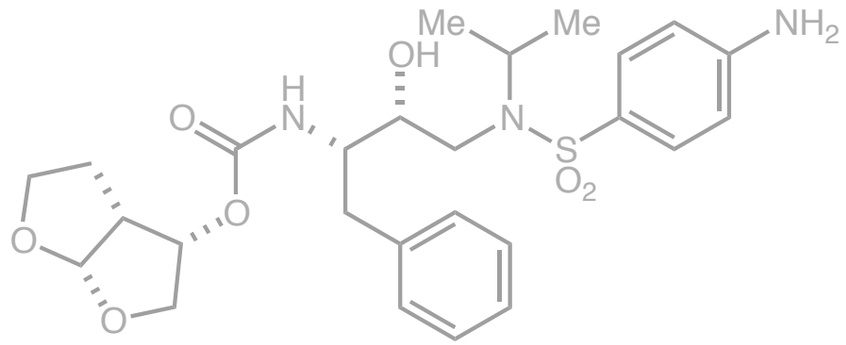
Methyldopa



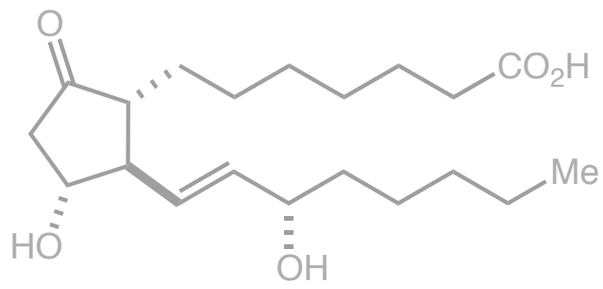
Imipenem



Efavirenz

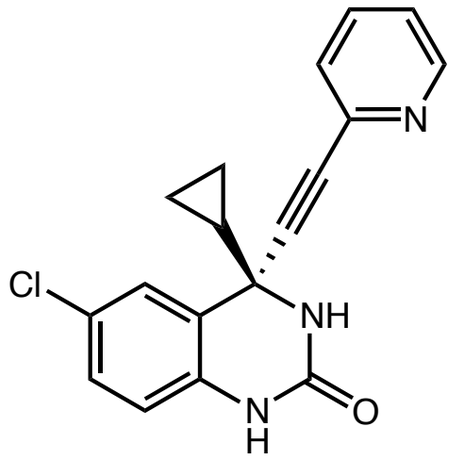


Darunavir

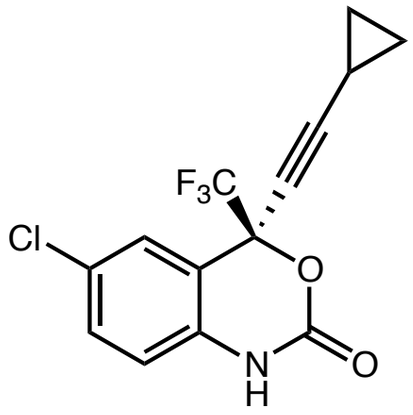


Prostaglandin E_1

Mechanistic and Synthetic Studies towards the Production of Efavirenz



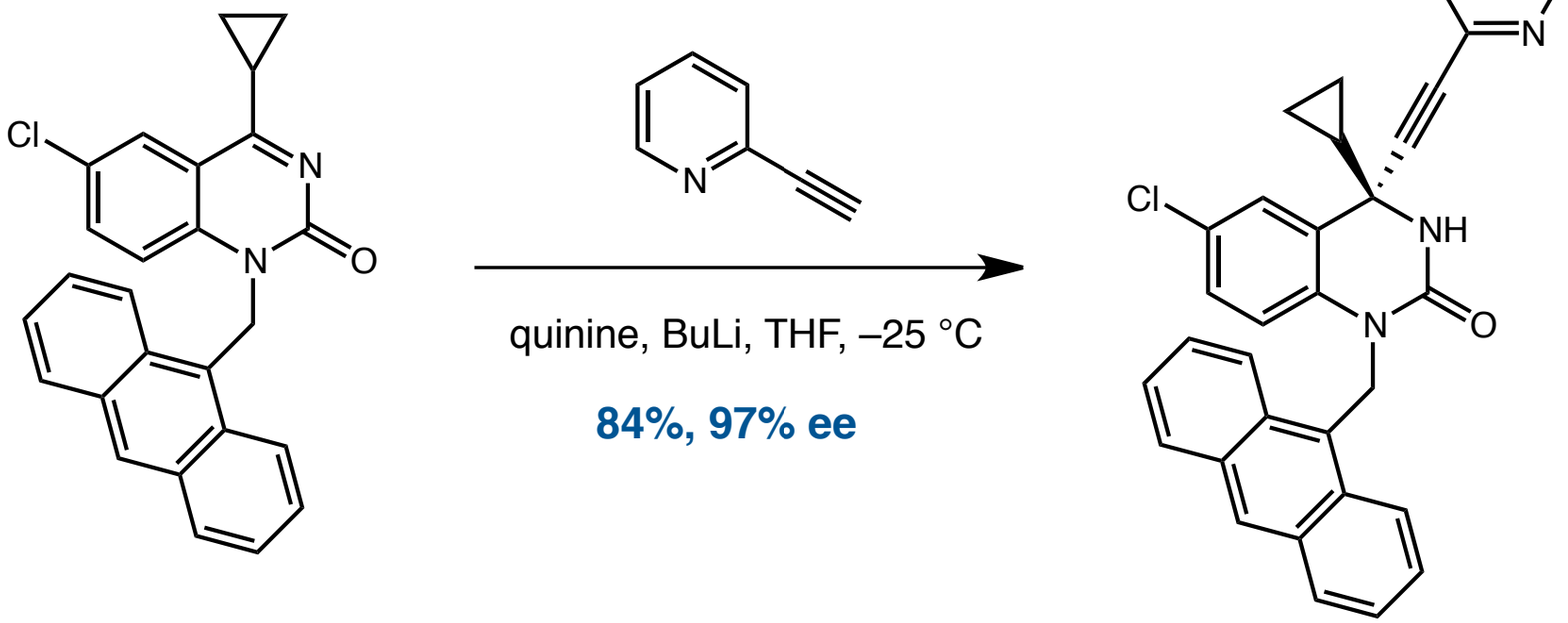
L-738, 372



Efavirenz

non-nucleoside reverse transcriptase inhibitor for HIV type 1

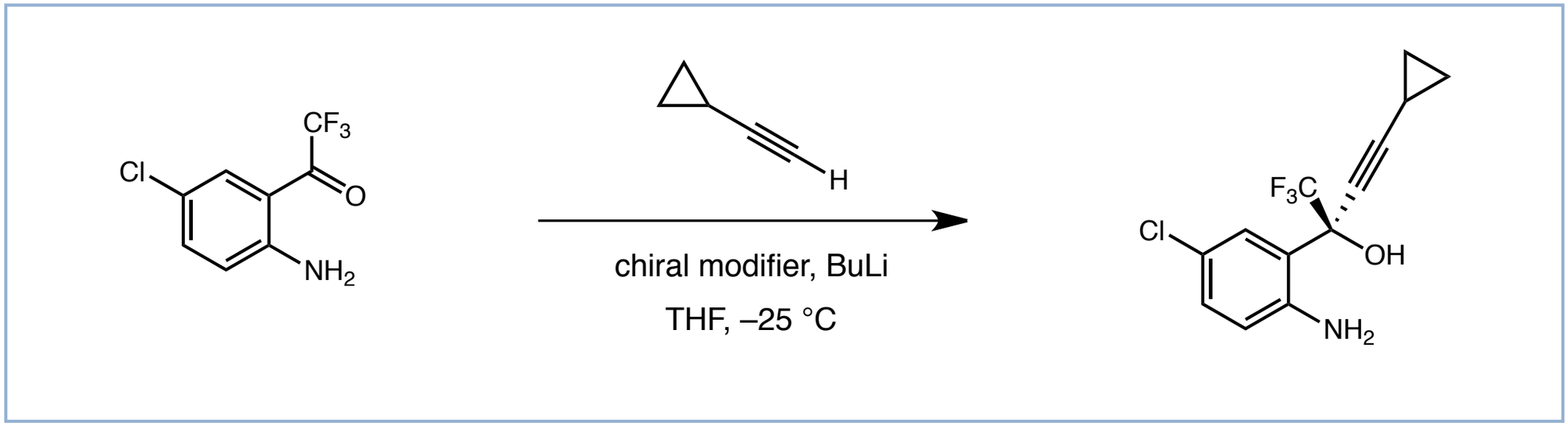
sold in combination with tenofovir, emtricitabine: Atripla since 2006



collaboration between Merck Process and Dave Collum at Cornell

Development of efficient and enantioselective acetylide addition

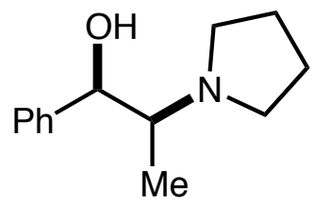
Mechanistic and Synthetic Studies towards the Production of Efavirenz



chiral modifier	conversion (%)	ee (%)
quinine	6	72
N-Me-pseudoephedrine	29	67
N-Me-ephedrine	62	72

N-protecting group: *p*-methoxybenzyl

amino alcohol:



Key Observations

2 equivalents of ephedrine and acetylide were required for complete conversion

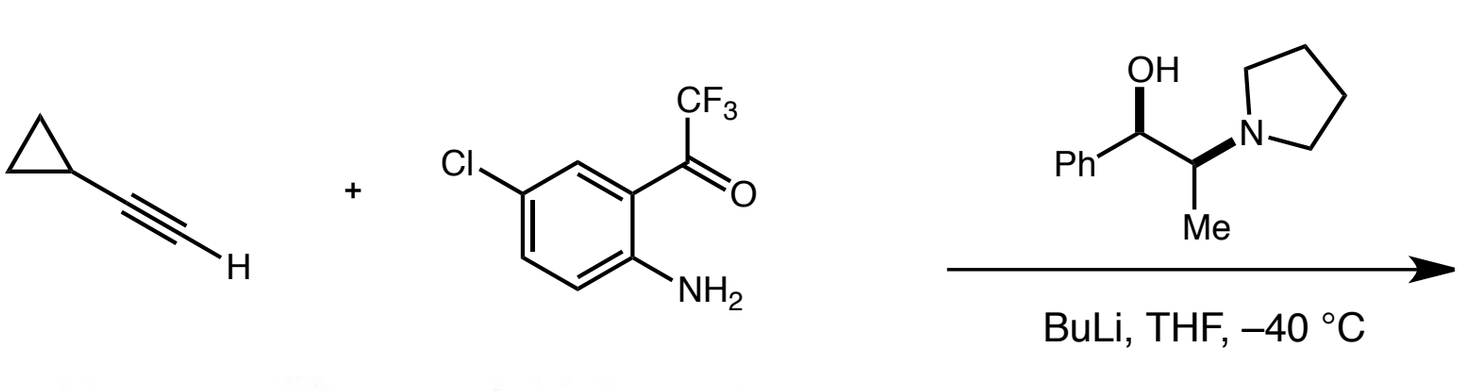
Pre-equilibration Temp (° C)	ee (%)
–40 °C	80 (avg)
0 °C	>98

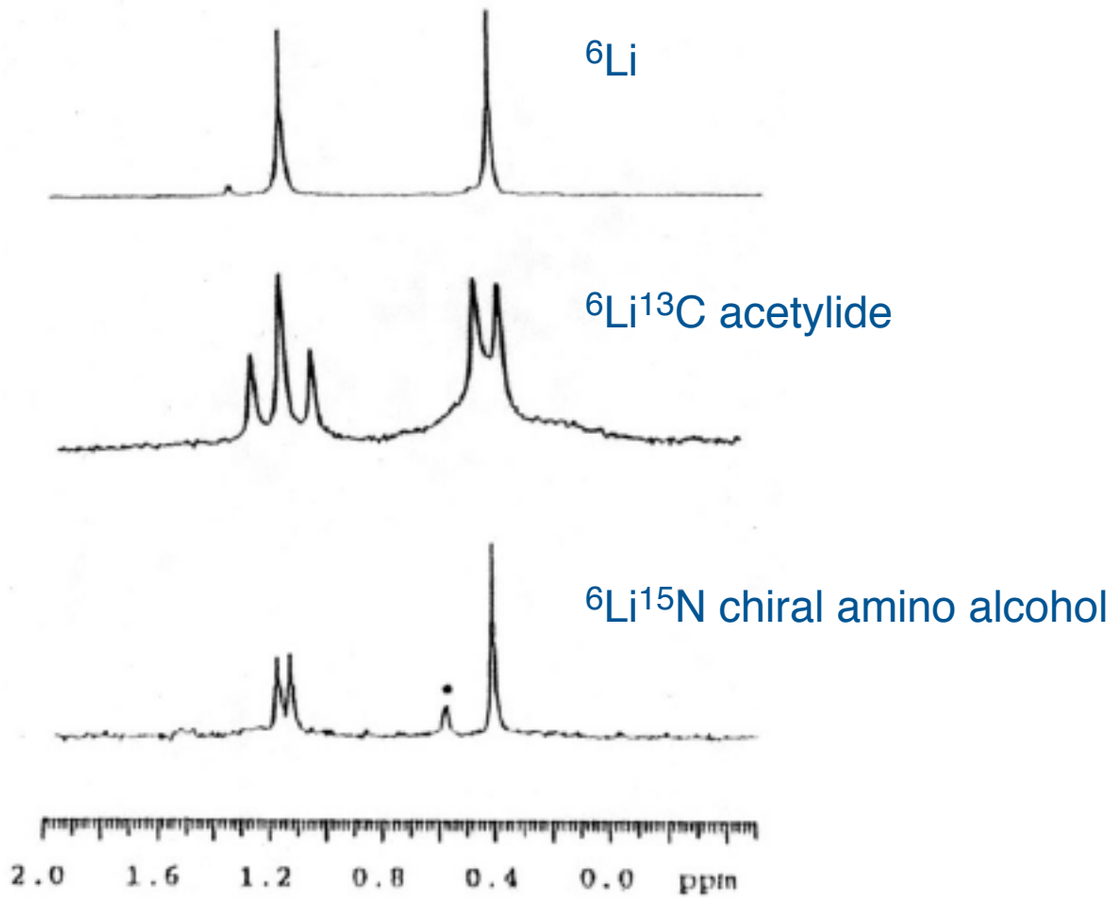
Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tet. Lett*, **1995**, *36*, 8937

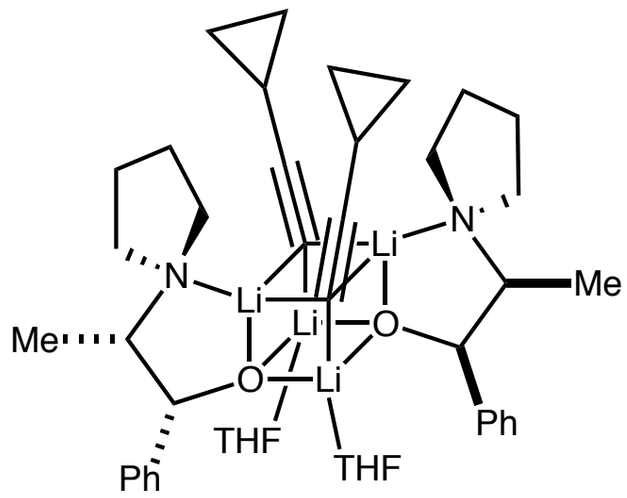
Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J.F.; Collum, D. B. *J. Am. Chem. Soc.*, **1998**, *120*, 2028

Mechanistic and Synthetic Studies towards the Production of Efavirenz

collaboration with Dave Collum at Cornell







proposed Li-tetramer

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Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J.F.; Collum, D. B. *J. Am. Chem. Soc.*, **1998**, *120*, 2028

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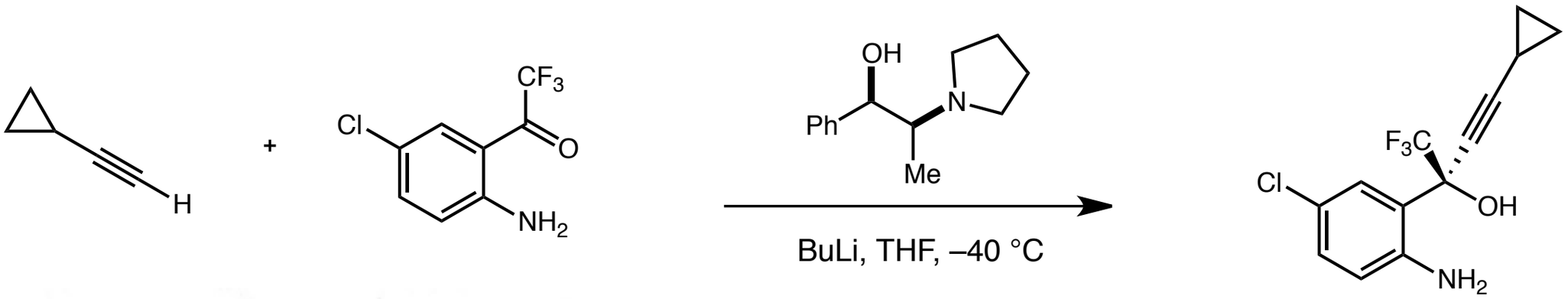
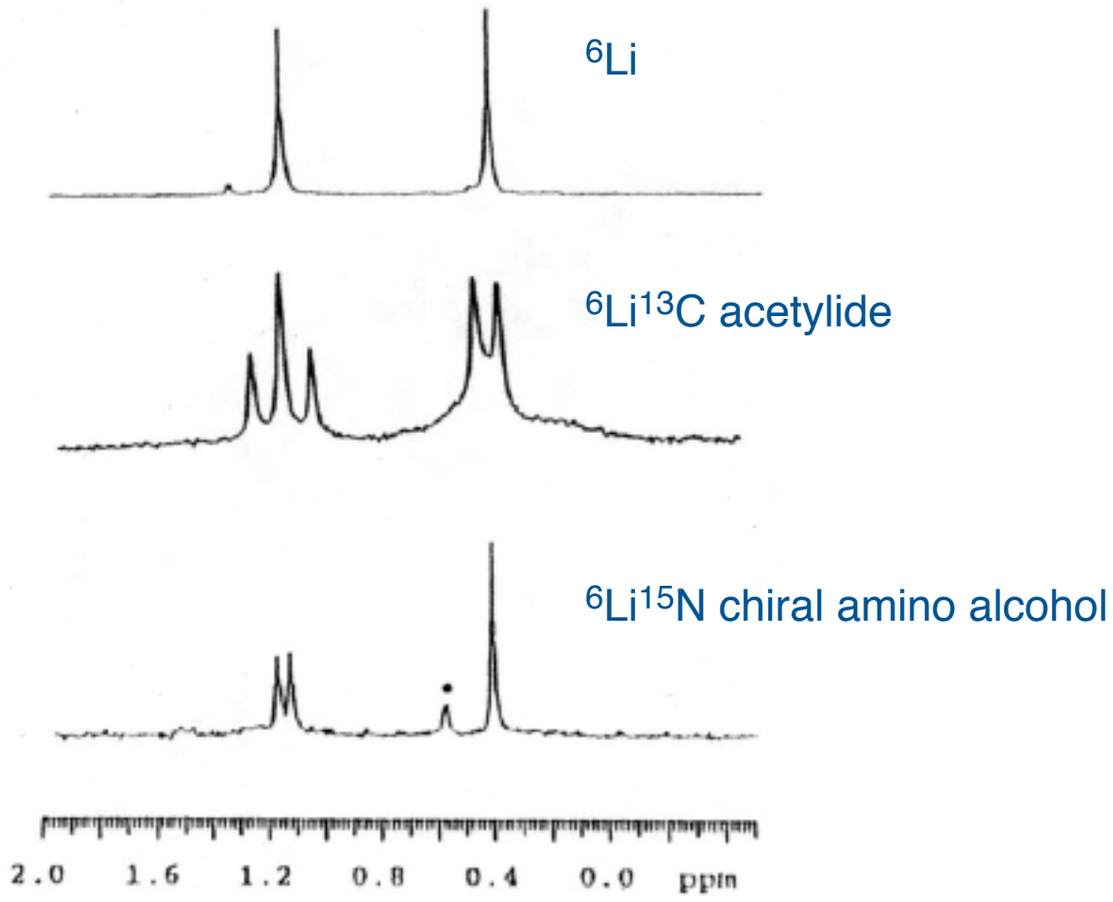
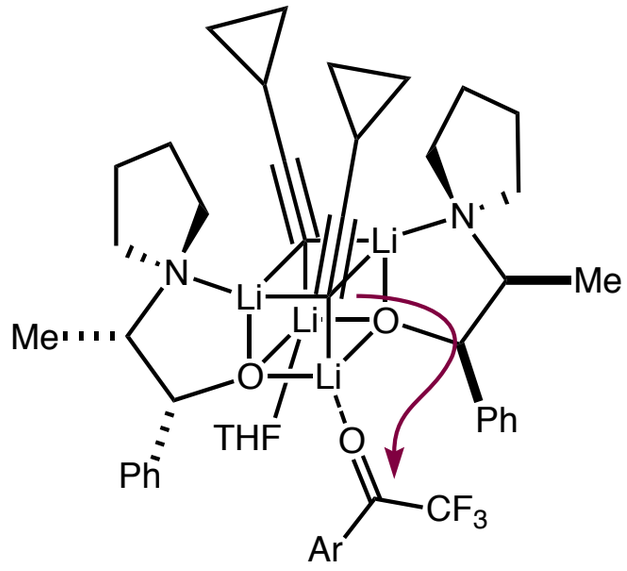






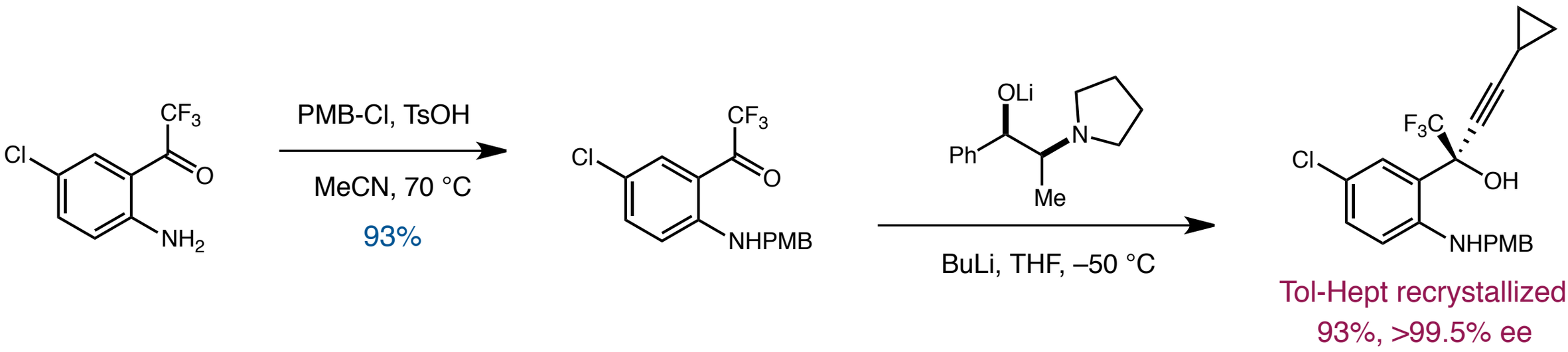
acetylide delivery to *re*-face
as predicted by tetramer structure

Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tet. Lett*, **1995**, *36*, 8937

Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J.F.; Collum, D. B. *J. Am. Chem. Soc.*, **1998**, *120*, 2028

Mechanistic and Synthetic Studies towards the Production of Efavirenz

synthesis of Efavirenz



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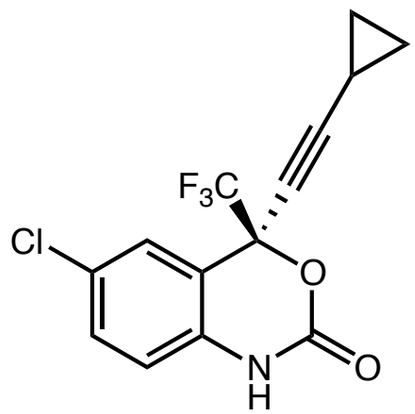
Mechanistic and Synthetic Studies towards the Production of Efavirenz



Efavirenz

- combination therapy Atripla combines Efavirenz, tenofovir, emtricitabine
- expedient synthesis allows for inexpensive manufacturing process

  sold in developing countries for about $1/day
- productive collaboration between industry and academia

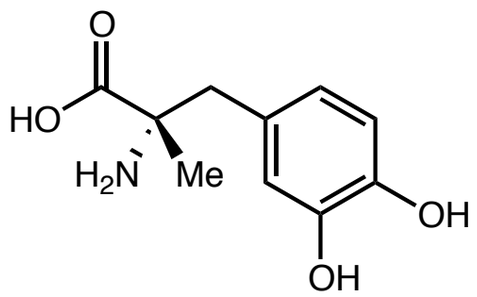
Edward Grabowski, Ph.D.

Prof. David Collum

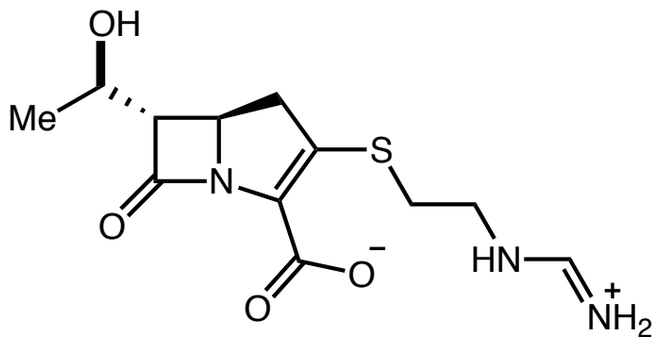
"As to our interactions with Dave Collum, I can only say that he is a prince among chemists, and he has changed the ways in which we view all lithium anion reactions." - Ed Grabowski

Grabowski, E. J. J. *ACS Symposium Series*, **2004**, 870 (Chemical Process Research)

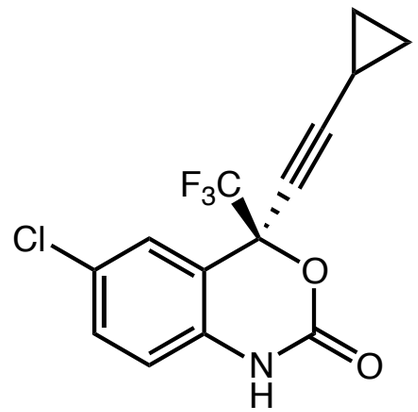
Classic Syntheses in Pharmaceutical Process Research and Development



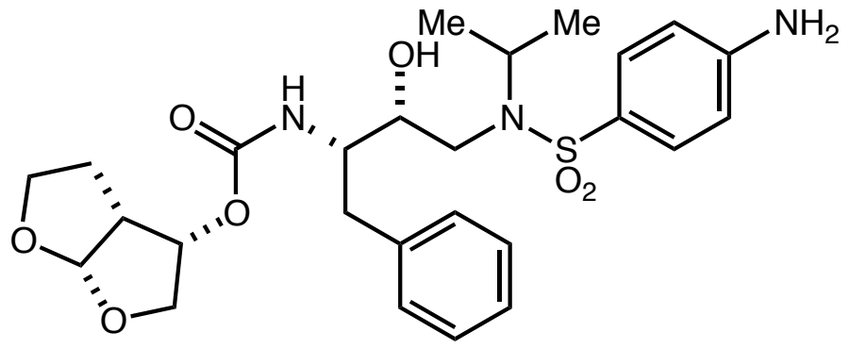
Methyldopa



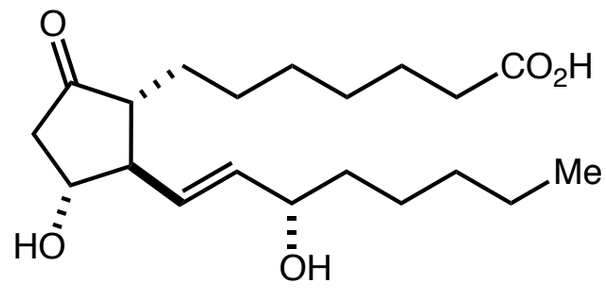
Imipenem



Efavirenz

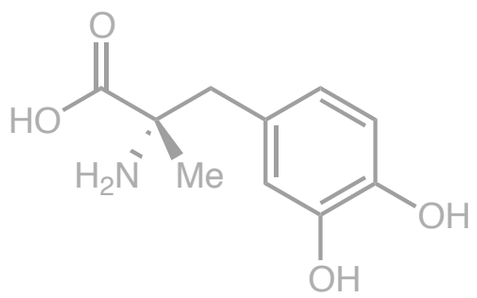


Darunavir

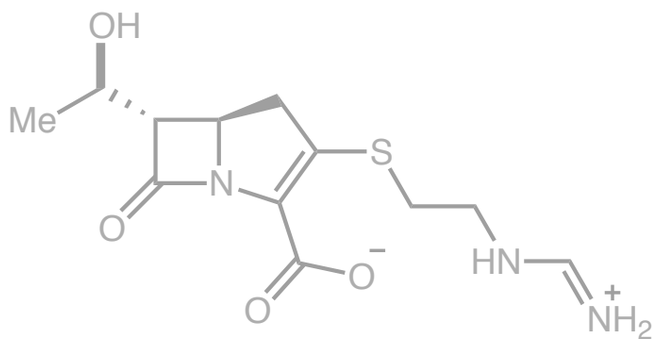


Prostaglandin E_1

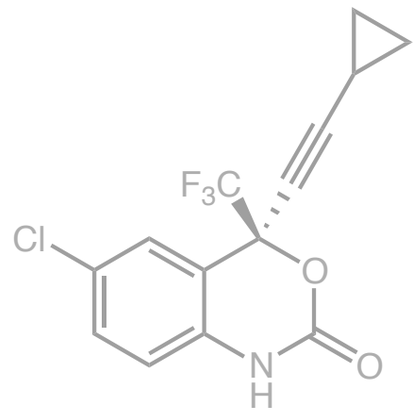
Classic Syntheses in Pharmaceutical Process Research and Development



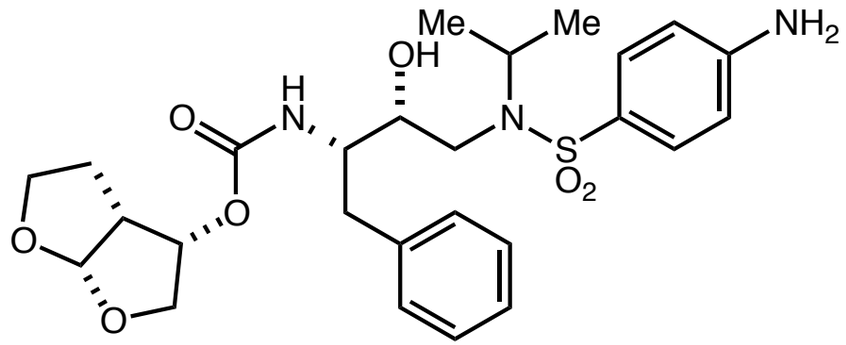
Methyldopa



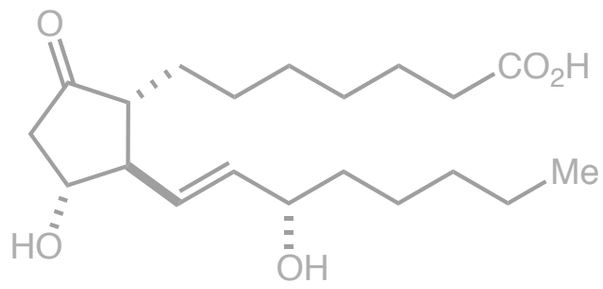
Imipenem



Efavirenz



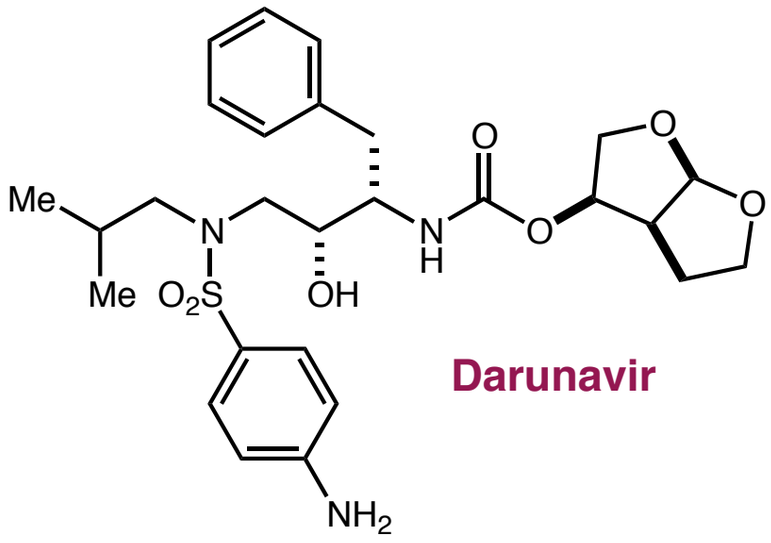
Darunavir



Prostaglandin E_1

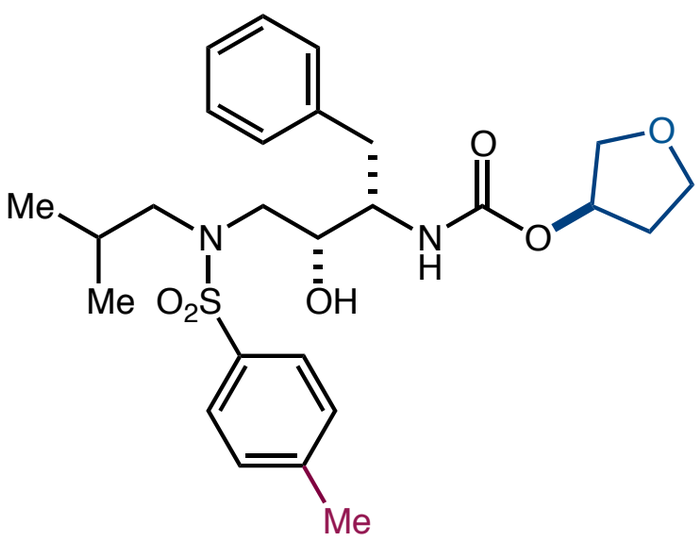
The Tibotec Synthesis of Darunavir

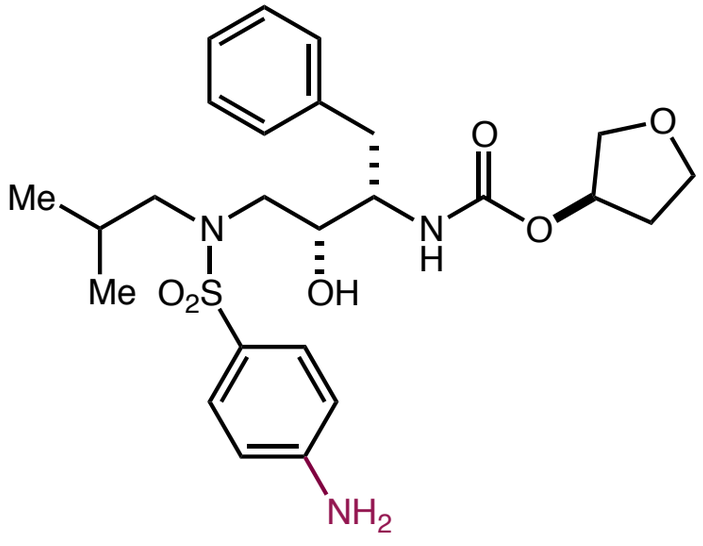
Addressing Resistance Towards Peptide-based HIV Protease Inhibitors

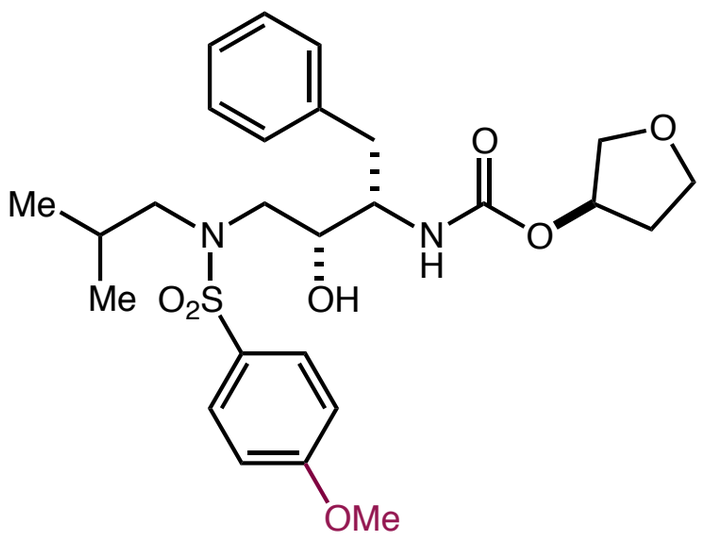


Darunavir

- 1990's HIV resistance to protease inhibitors
- eliminate peptide-like character
- Ghosh et al. developed novel biological mimics of peptide-like structures
- stereochemically defined and conformationally constrained





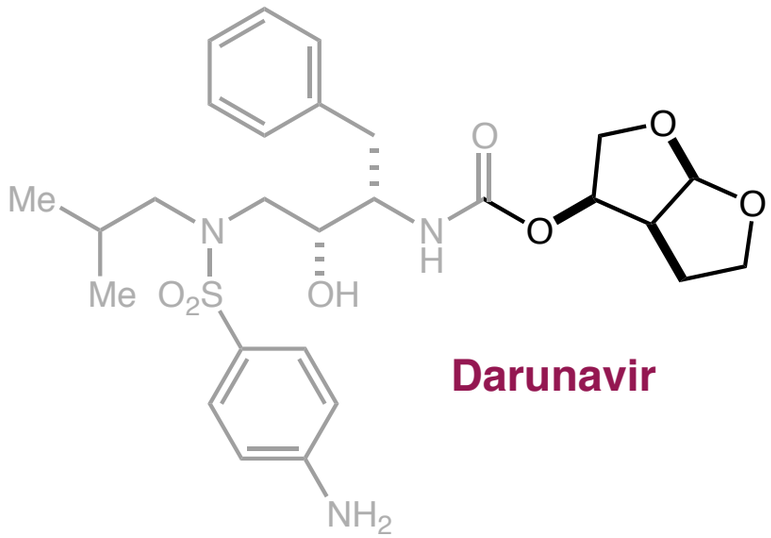


SAR developed at Dept of Chemistry, University of Illinois at Chicago, The Chicago Medical School

Ghosh, A. K.; Kincaid, J. F.; et. al. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 687

The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol

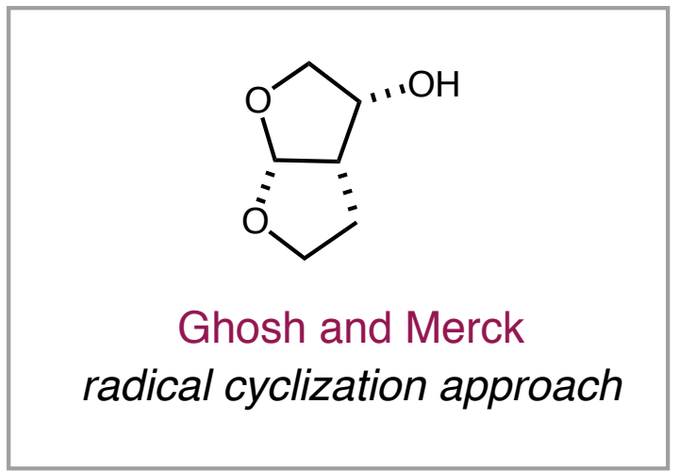


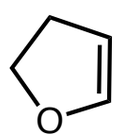
Darunavir

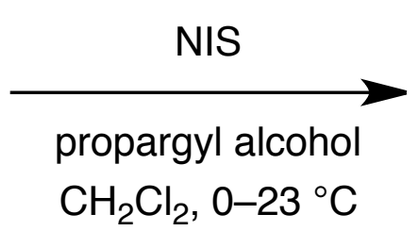
Ghosh, A. K.; Kincaid, J. F.; et. al. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 687

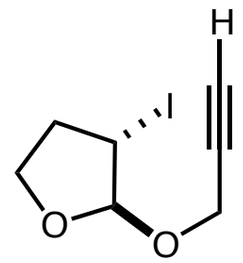
The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol

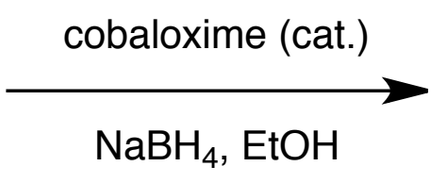


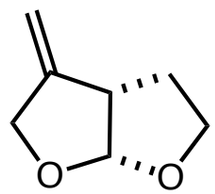




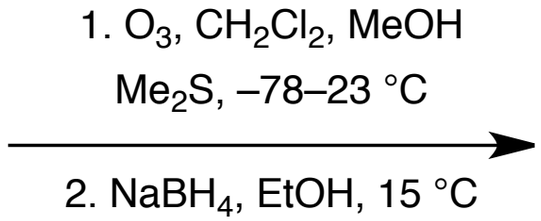


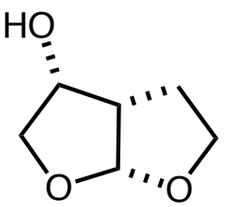
91%





75%





78%

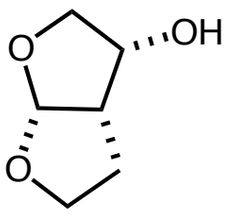
chiral resolution provides 95% ee of alcohol

expensive and unscalable radical cyclization

Ghosh, A. K.; Kincaid, J. F.; et. al. *J. Med. Chem*, **1996**, *39*, 3278

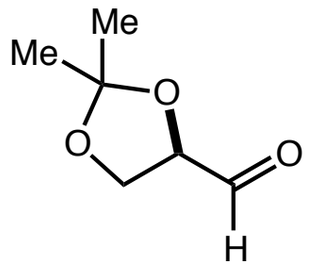
The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol



Ghosh

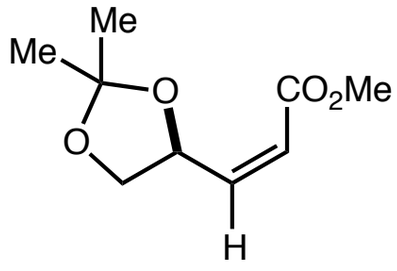
photochemical conjugate addition



$Ph_3P{=}CHCO_2Me$

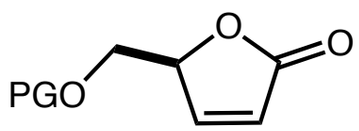
MeOH, 0 °C

88%



H_2SO_4, MeOH

then protection



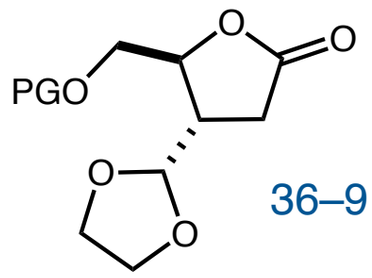
75%

benzophenone

(10–15 mol%)

Hg-lamp

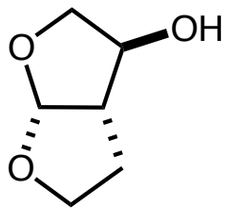
[1,3]-dioxolane



36–91%

1. LAH, THF

2. 1N HCl, THF/H_2O



77%

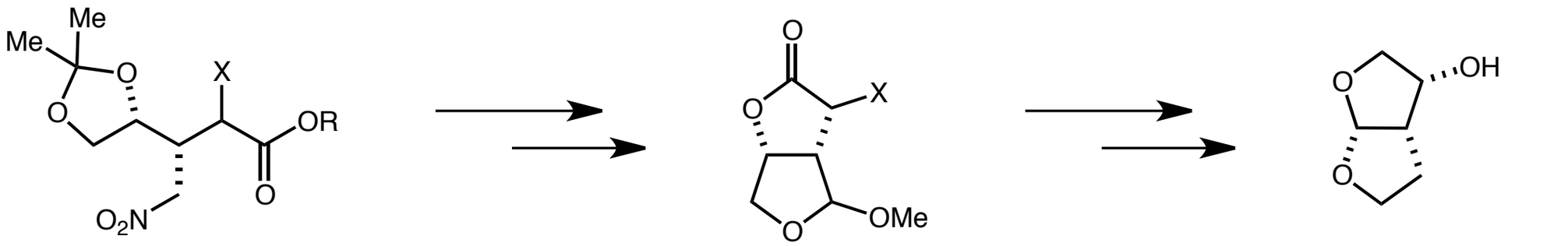
R=Bn

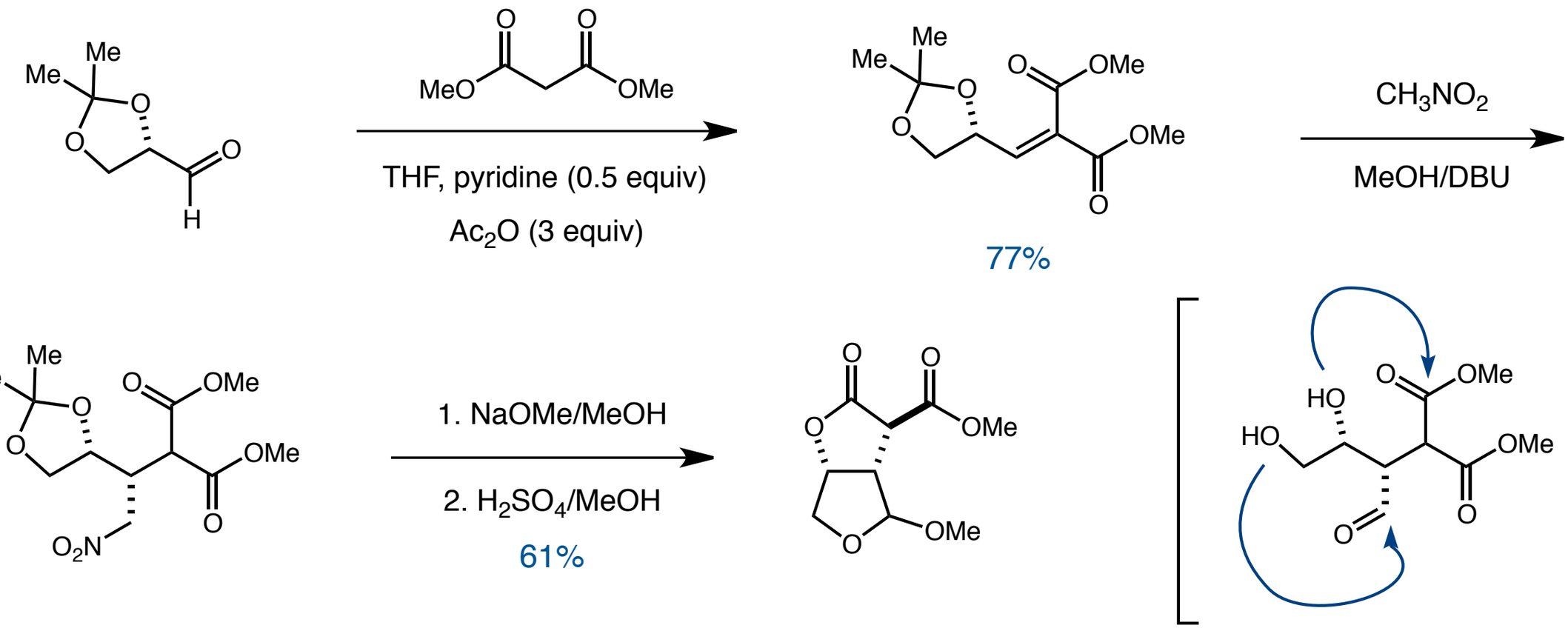
difficult to scale photochemical reactions

reduction provides incorrect diastereomer

Ghosh, A. K.; Leschenko, S.; Noetzel, M. *J. Org. Chem*, **2004**, *69*, 7822

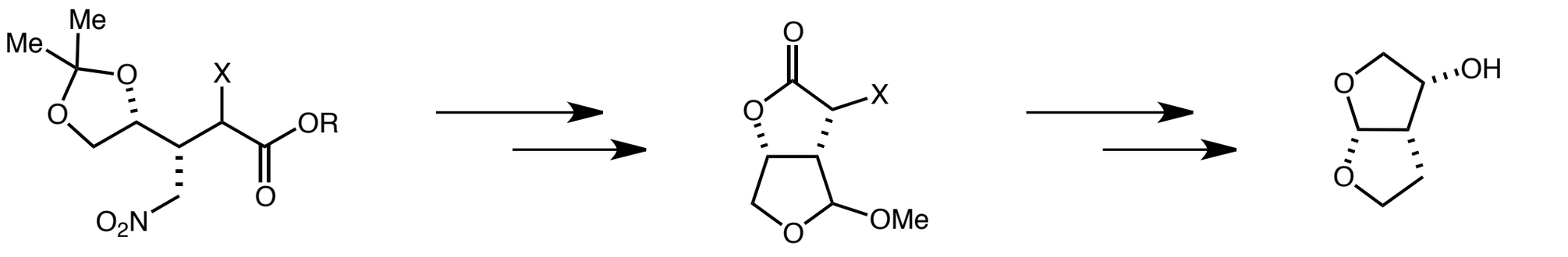
The Tibotec Synthesis of Darunavir

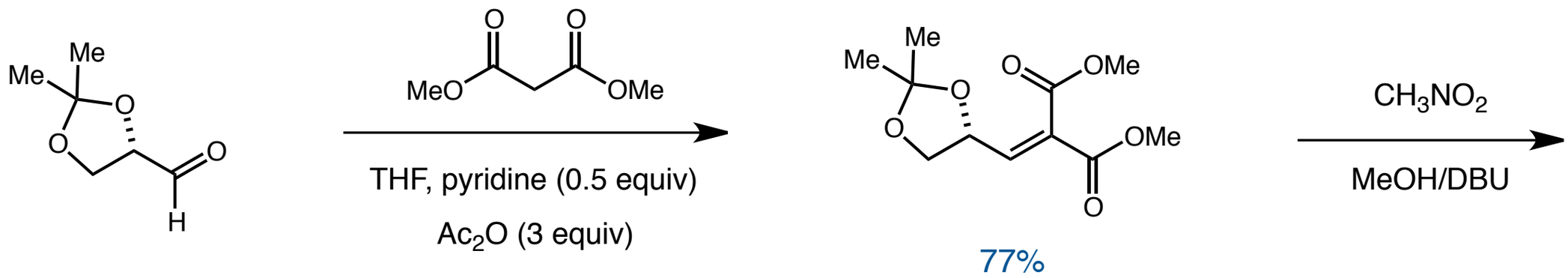


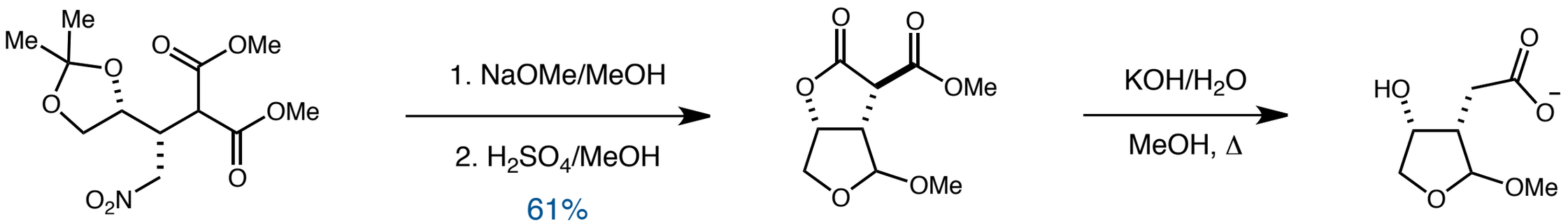


Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.,* **2005**, *7*, 5917

The Tibotec Synthesis of Darunavir







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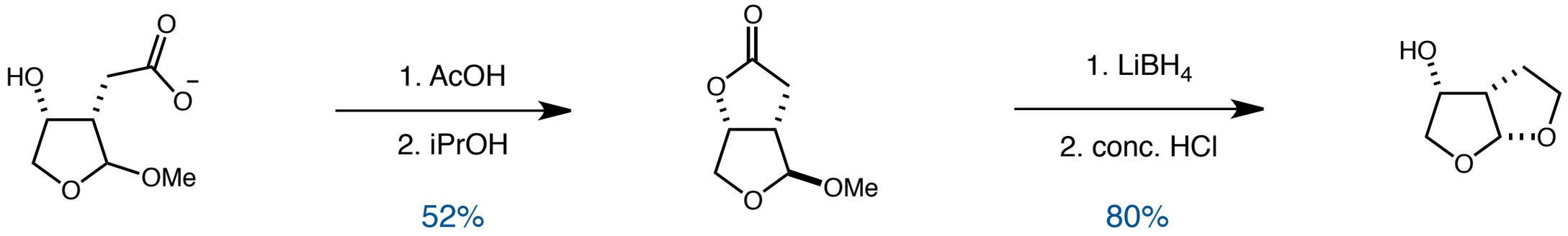
The Tibotec Synthesis of Darunavir

Completing the 6-step route to key pharmacophore



6 steps, 19% overall yield **produced over 100kg of material**

drawbacks: Knoevenagel reaction maximum yield is 77%

decarboxylation/recyclization loses 50% of material

required large reactors due to intermediate lability

Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.,* **2005**, *7*, 5917

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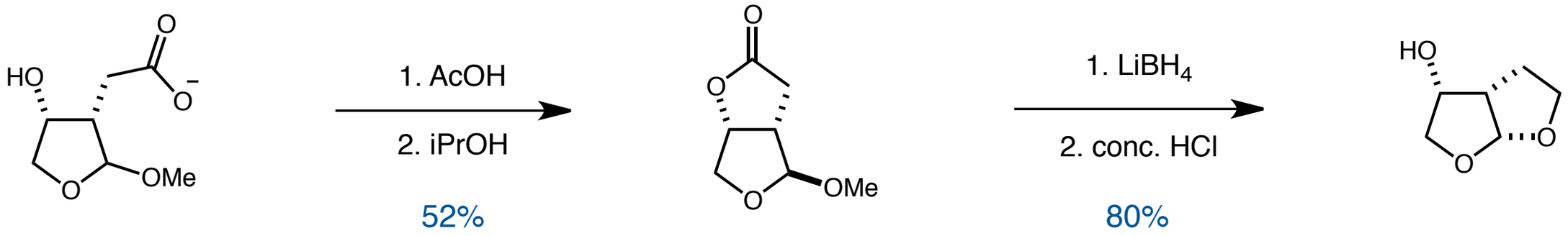
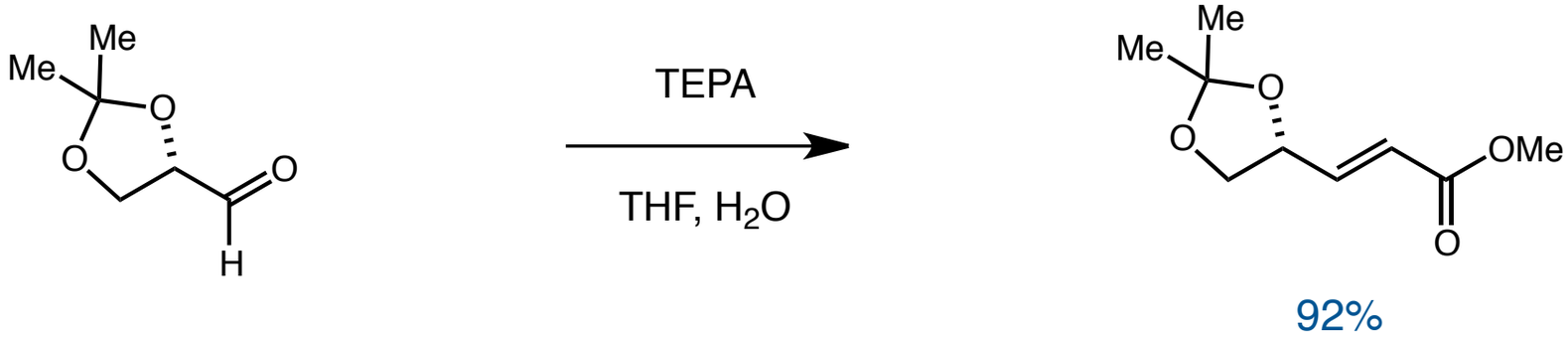


6 steps, 19% overall yield **produced over 100kg of material**

Horner-Wadsworth-Emmons



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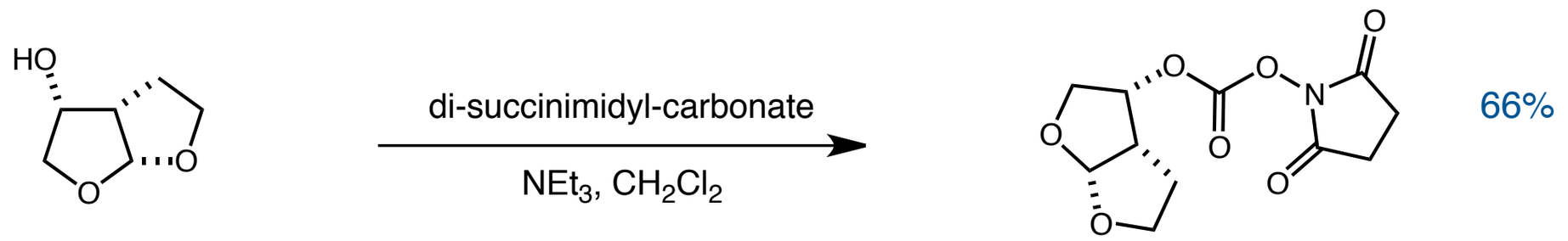
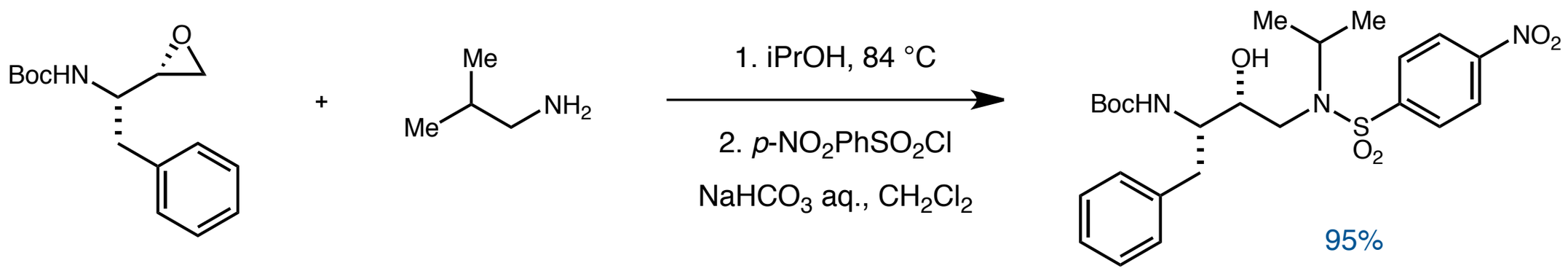
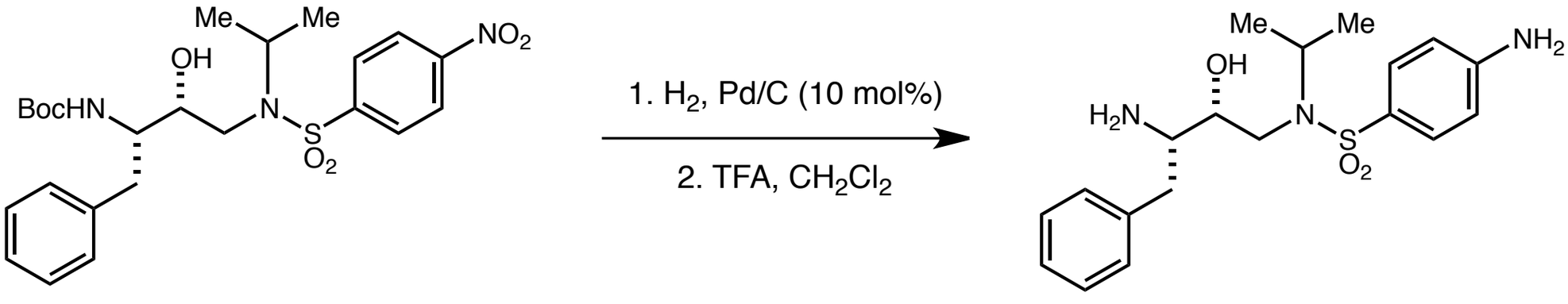
The Tibotec Synthesis of Darunavir

End-Game adopted from Ghosh's early synthesis







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The Tibotec Synthesis of Darunavir

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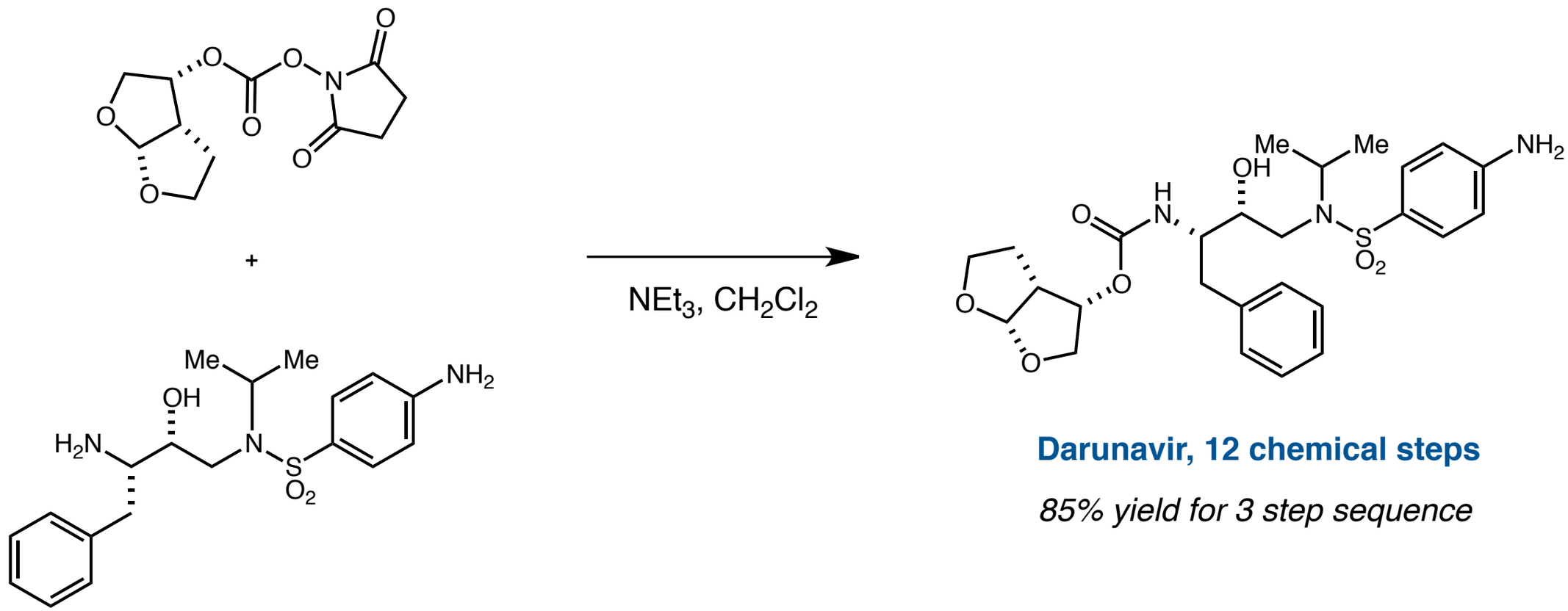

Approved in 2006 for multiply resistance HIV 1 infections

collaborations between U. I. Chicago, Merck, Tibotec and DSM Pharma

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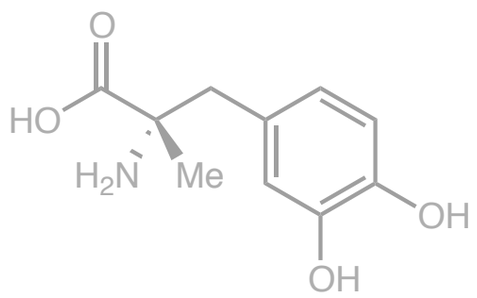
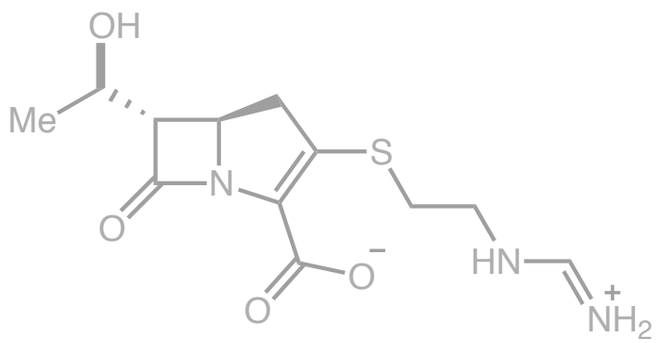
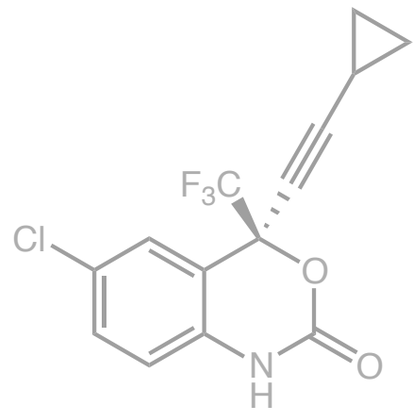
Classic Syntheses in Pharmaceutical Process Research and Development



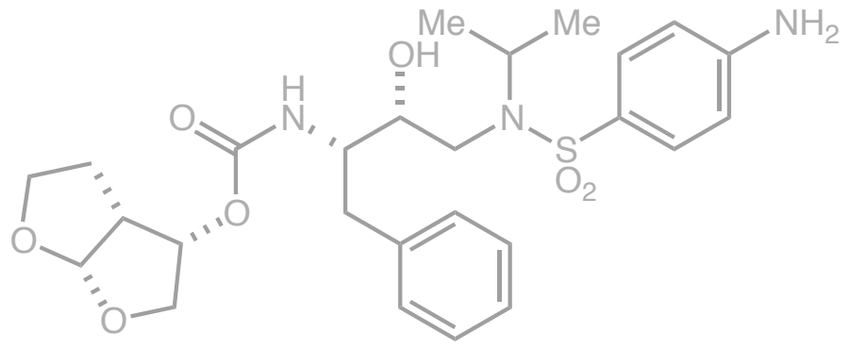
Methyldopa



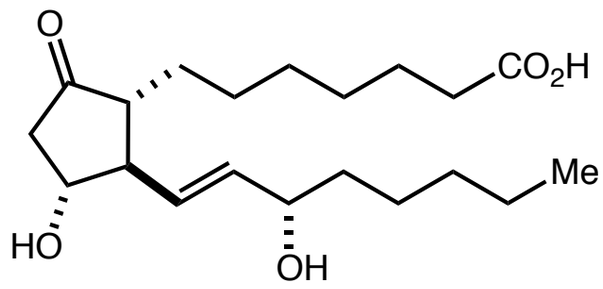
Imipenem



Efavirenz



Darunavir

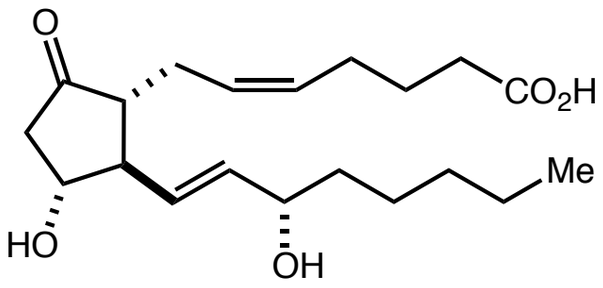


Prostaglandin E_1

The Syntex Synthesis of Prostaglandin PGE_1

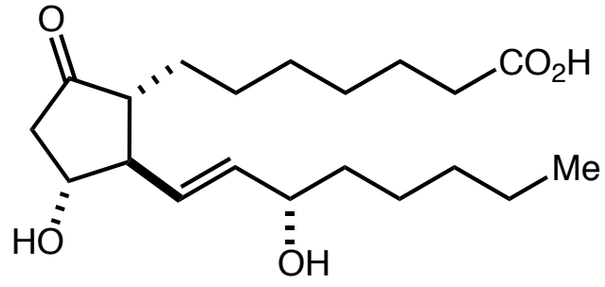
Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

PGE_2



Induces childbirth or abortion

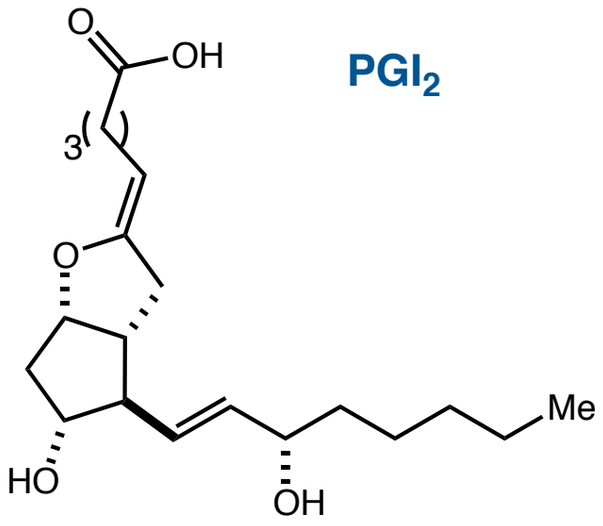
PGE_1



treatment of infant heart defects

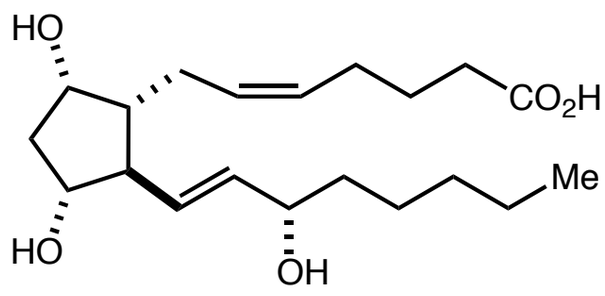
erectile dysfunction

PGI_2



vasodilation

$PGF_{2\alpha}$

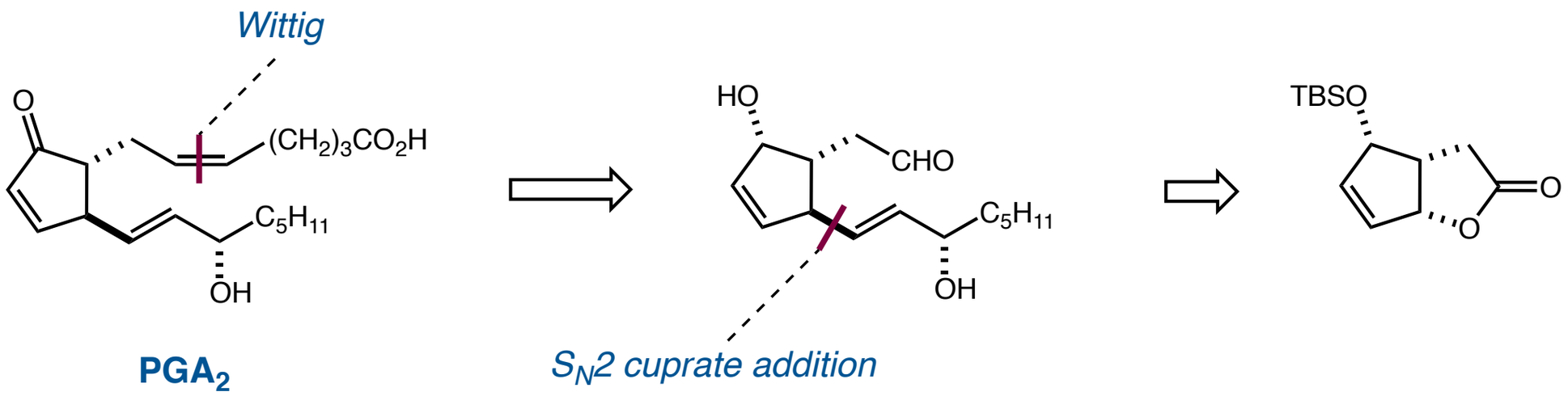


uteral contraction and bronchoconstriction

Bindra, J. S.; Bindra, R. (1977) *Prostaglandin Synthesis.* New York, New York: Academic Press. pp 2–6

The Syntex Synthesis of Prostaglandin PGE_1

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry



Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832.

Corey, E. J.; Cheng, X.-M. The Logic of Chemical Synthesis, John Wiley & Sons, New York, 1995, pp 38.

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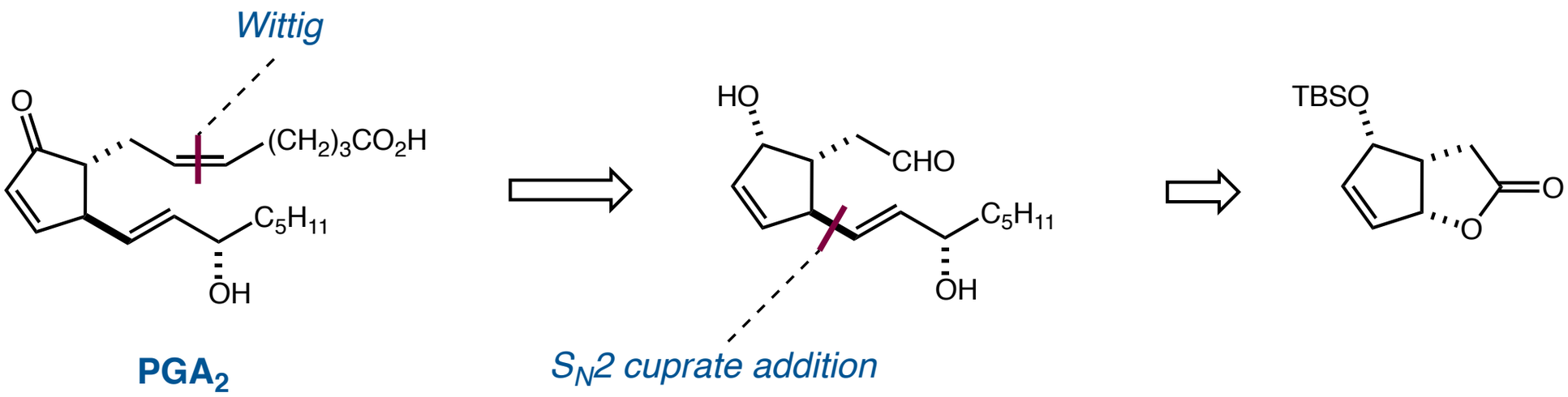
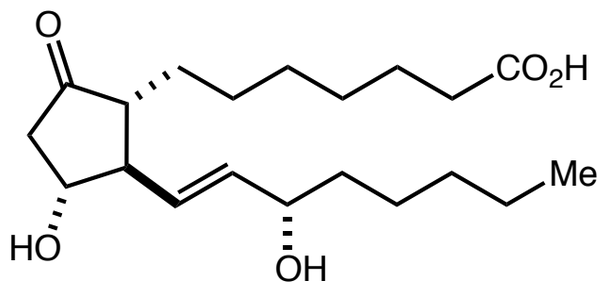


PGE_1



treatment of infant heart defects

erectile dysfunction

- Synthesis devised by Syntex Labs in Mexico
- Later acquired by Roche in Palo Alto
- Novel cuprate chemistry (heteratom-substitution)
- Modular and convergent synthesis

Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832.

Corey, E. J.; Cheng, X.-M. The Logic of Chemical Synthesis, John Wiley & Sons, New York, 1995, pp 38.

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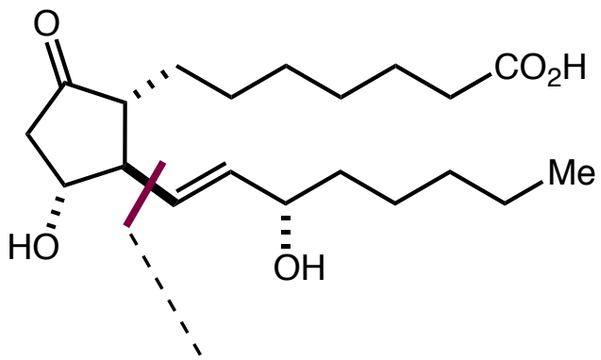
PGE_1



organocuprate conjugate addition

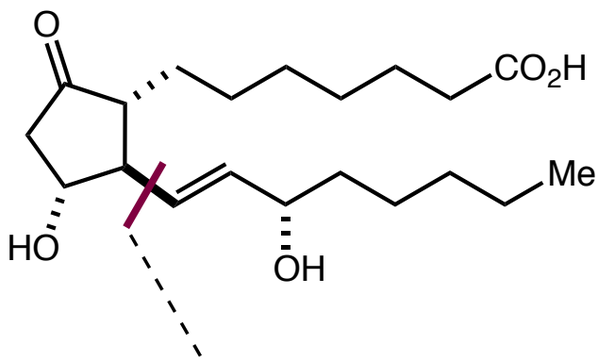
Patterson Jr., J. W.; Fried, J. H. *J. Org. Chem.,* **1974**, *39*, 2506

Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.,* **1972**, *94*, 7827

The Syntex Synthesis of Prostaglandin PGE_1

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

PGE_1



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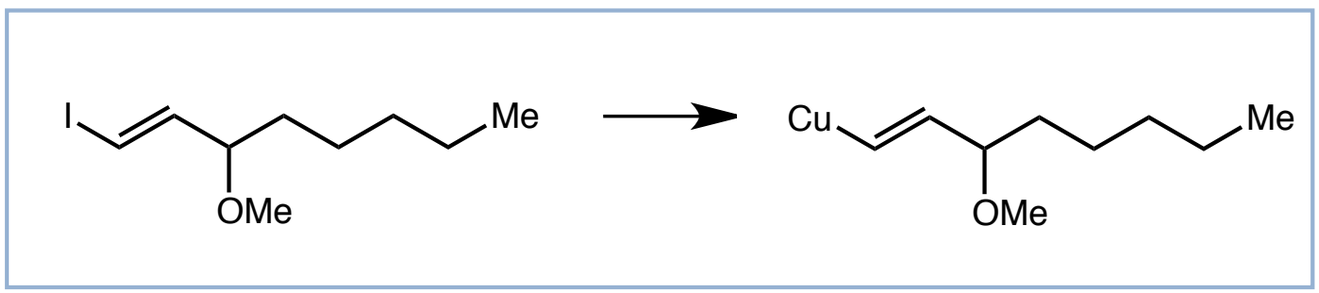

Cu(I) source	solvent	Temp (°C)	(% d)
$[EtO_3P]_2CuCN$	Et_2O	–70	0
CuI (0.5 equiv)	THF	–20	10

Patterson Jr., J. W.; Fried, J. H. *J. Org. Chem.,* **1974**, *39*, 2506

Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.,* **1972**, *94*, 7827

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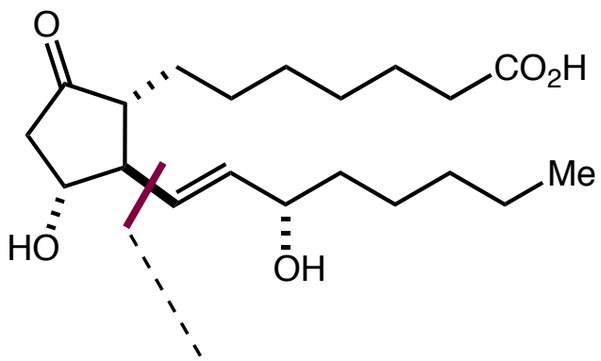
Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

PGE_1



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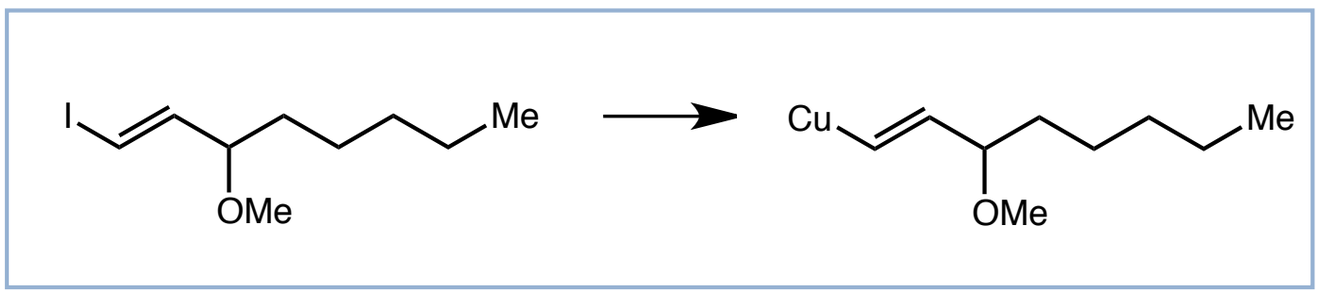

Cu(I) source	solvent	Temp (°C)	(% d)
$[EtO_3P]_2CuCN$	Et_2O	–70	0
CuI (0.5 equiv)	THF	–20	10
none	Et_2O	–20	88
CuI	Et_2O	–20	82
CuI (0.5 equiv)	Et_2O	–20	50
$[(Bu_3P)CuI]_4$	Et_2O	–70	71

low yields: 2–5%

Patterson Jr., J. W.; Fried, J. H. *J. Org. Chem.,* **1974**, *39*, 2506

Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.,* **1972**, *94*, 7827

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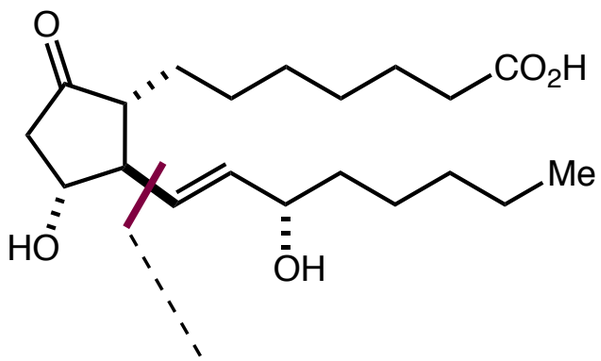
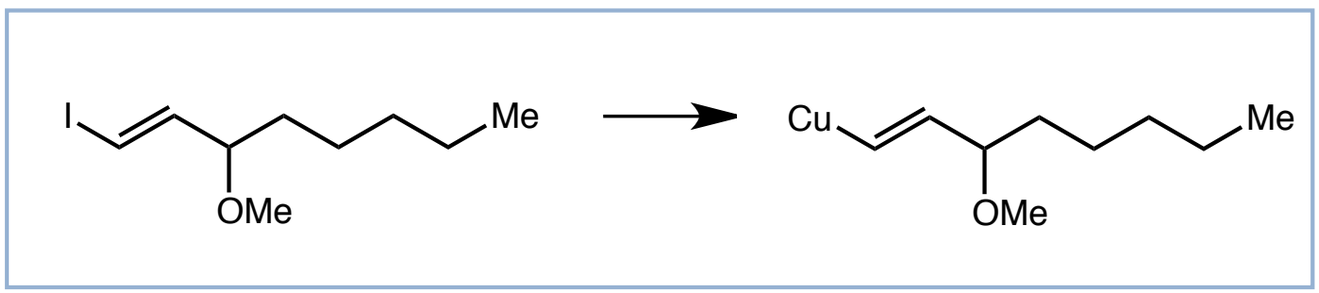


organocuprate conjugate addition



	Cu(I) source	solvent	Temp (°C)	(% d)
	$[EtO_3P]_2CuCN$	Et_2O	–70	0
	CuI (0.5 equiv)	THF	–20	10
	none	Et_2O	–20	88
	CuI	Et_2O	–20	82
	CuI (0.5 equiv)	Et_2O	–20	50
	$[(Bu_3P)CuI]_4$	Et_2O	–70	71
TMEDA **80%**	none	Et_2O	–20	85
	CuI	Et_2O	–20	76
	CuI (0.5 equiv)	THF	–20	67

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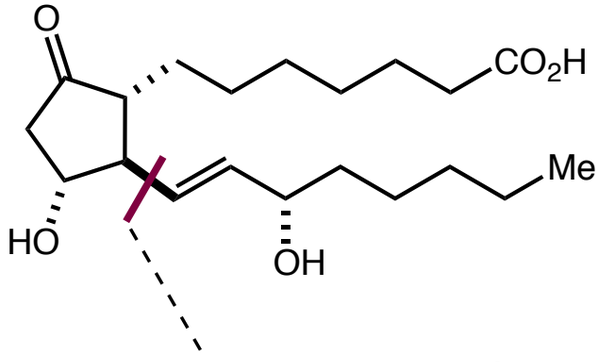
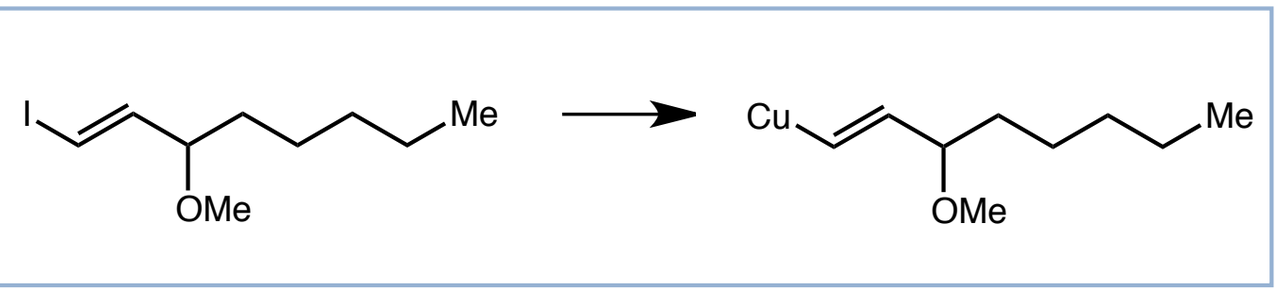
The Syntex Synthesis of Prostaglandin PGE_1

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

PGE_1



organocuprate conjugate addition



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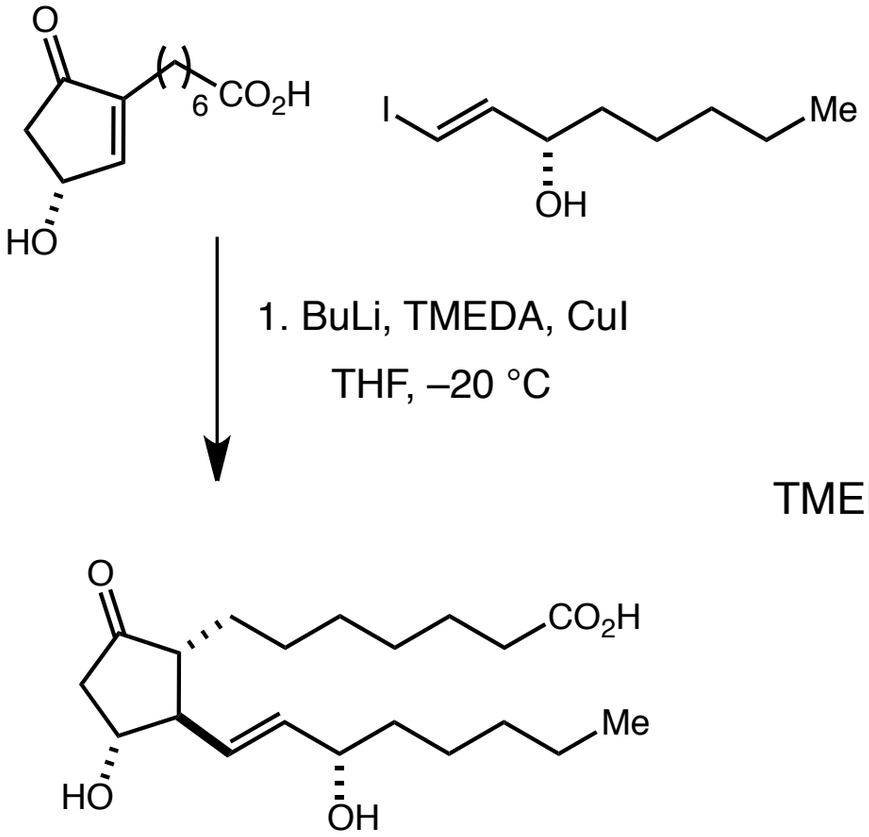

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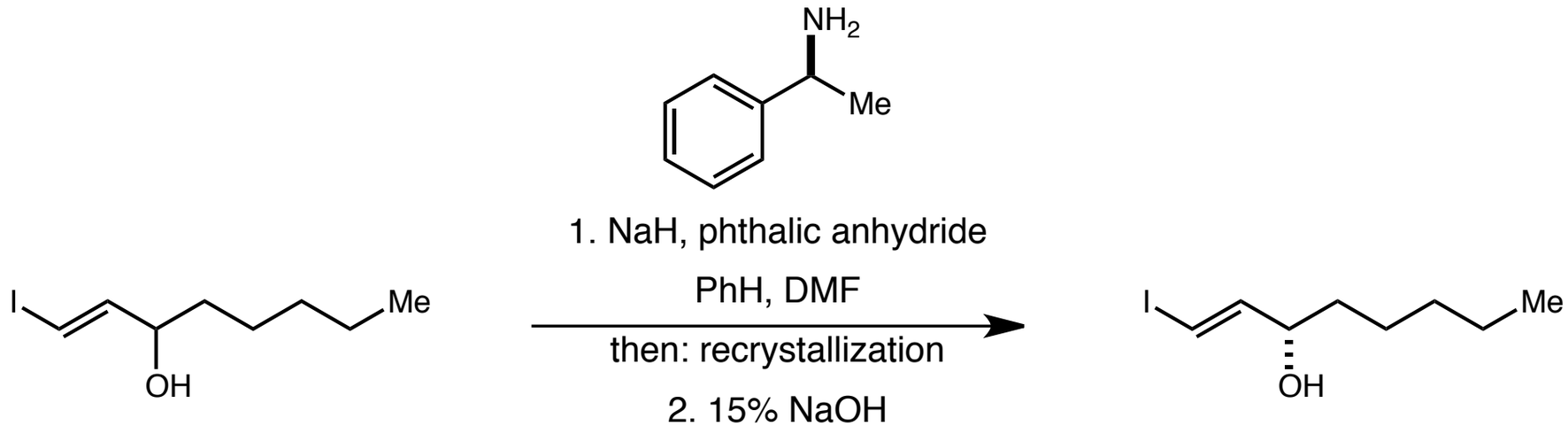

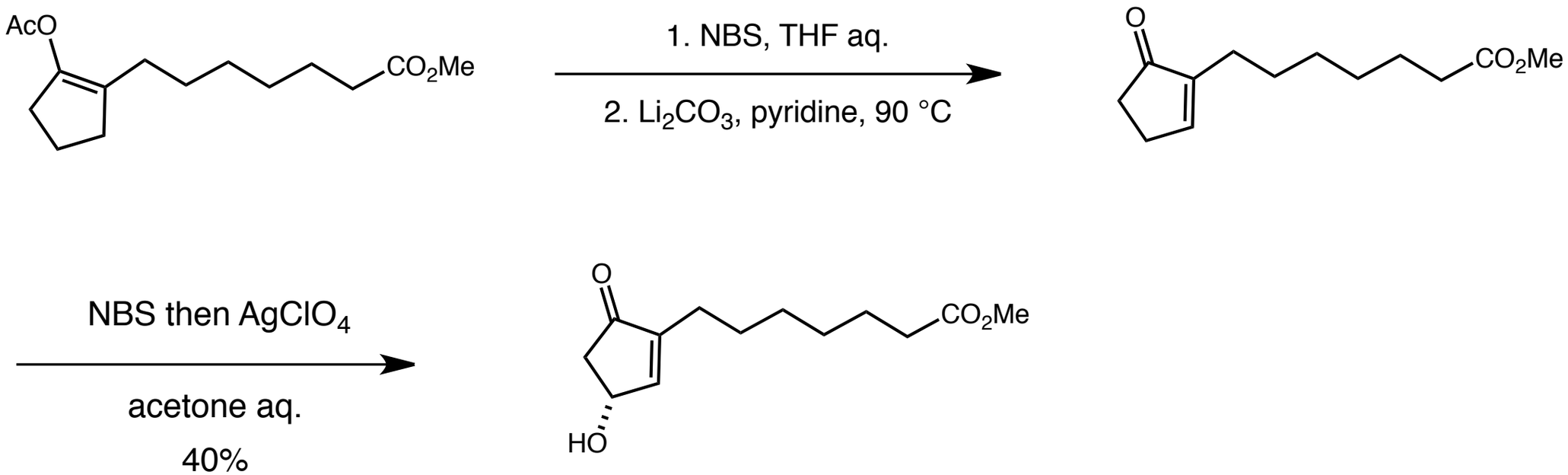

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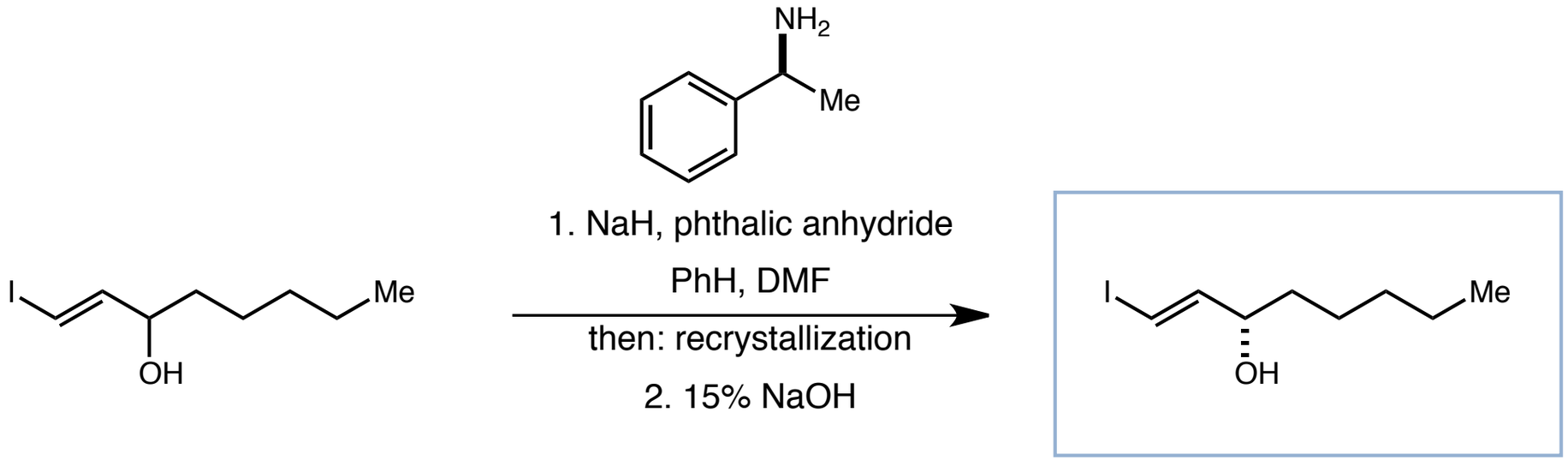

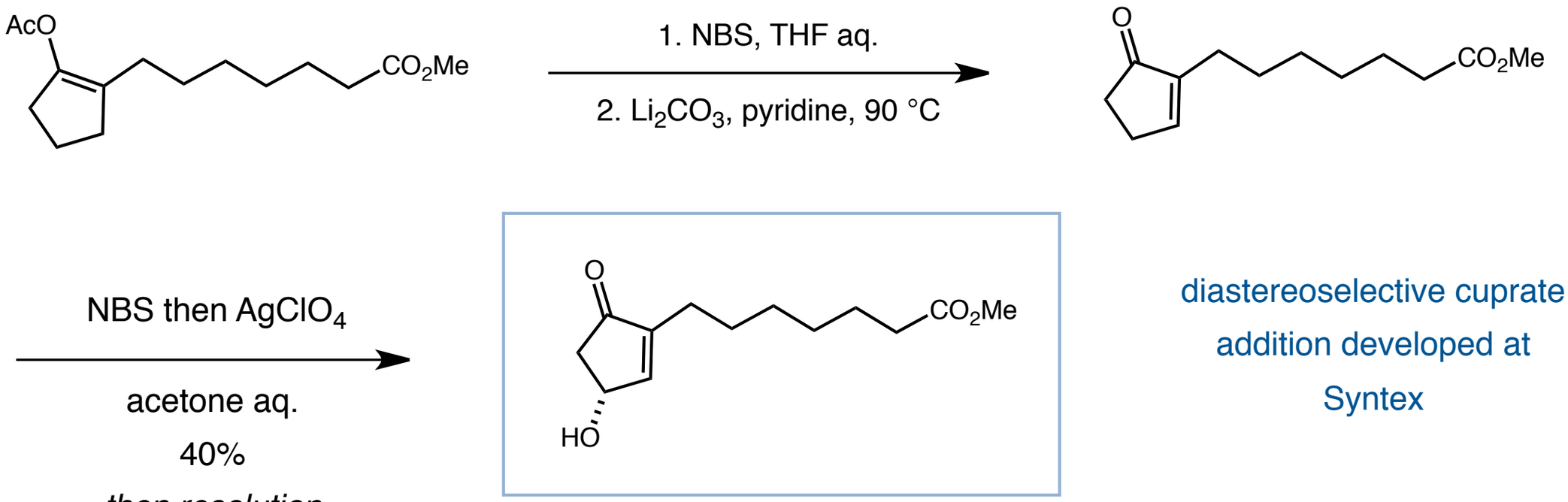

diastereoselective cuprate addition developed at Syntex

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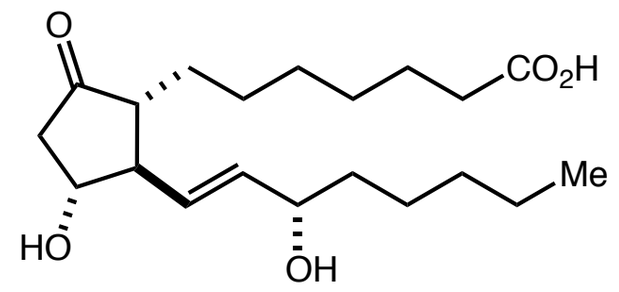
The Syntex Synthesis of Prostaglandin PGE_1

PGE_1



treatment of infant heart defects

erectile dysfunction

one of the shortest prostaglandin syntheses at 7 steps

elegent demonstration of atom economy in classical atom-uneconomical reaction

"green chemistry" before green chemistry was *cool*

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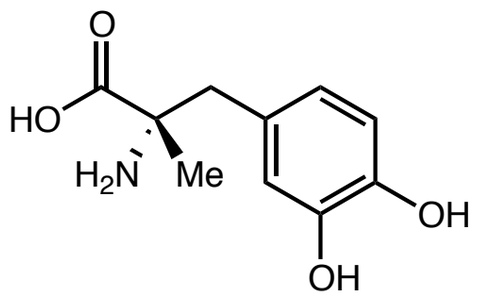
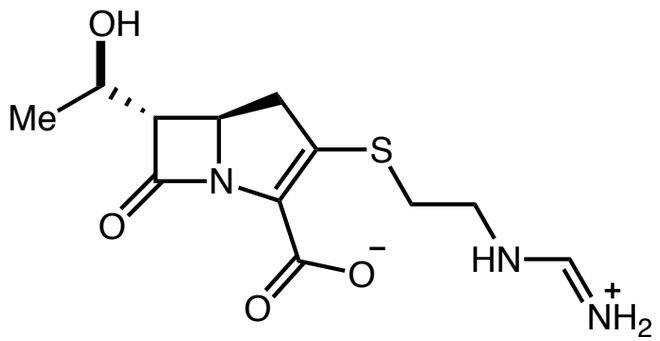
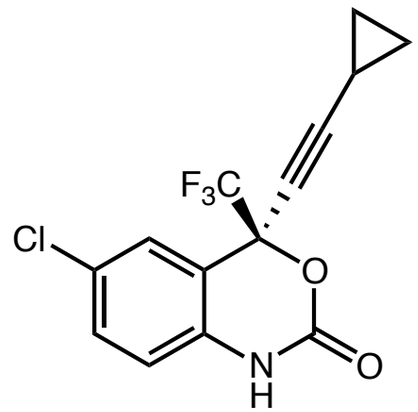
Classic Syntheses in Pharmaceutical Process Research and Development



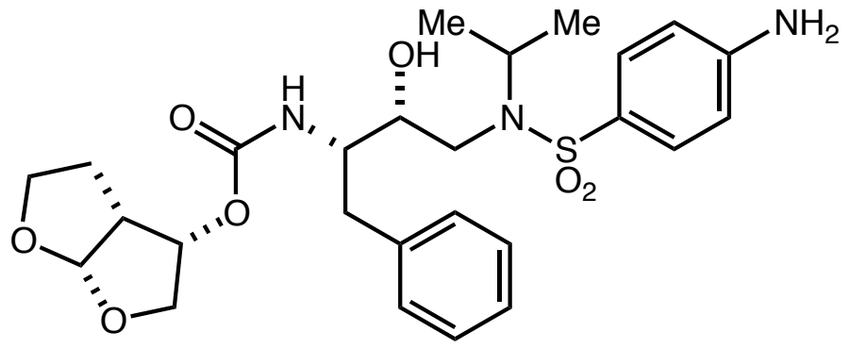
Methyldopa



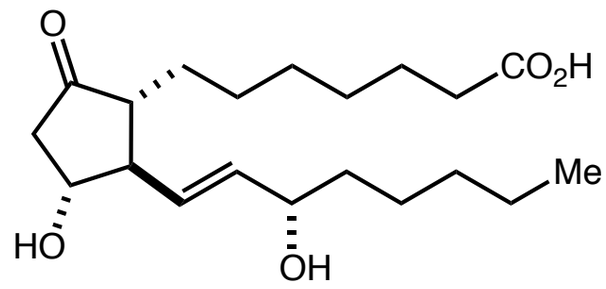
Imipenem



Efavirenz



Darunavir



Prostaglandin E_1