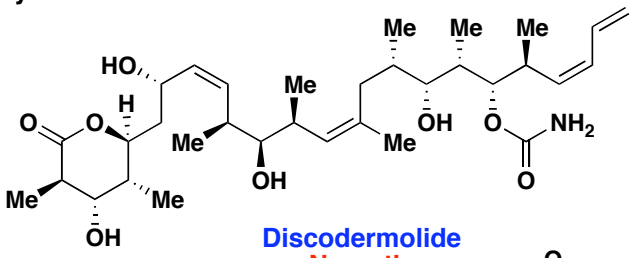
Richter

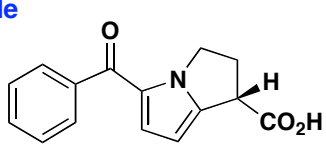
Masterpieces in Process Chemistry

11/3/04
Group Meeting

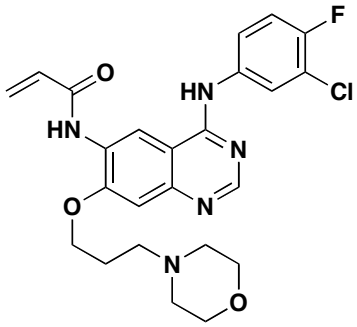
Selected Syntheses Discussed:



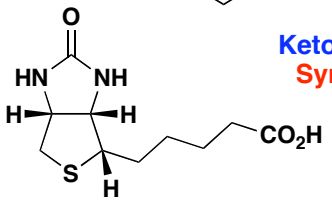
Discodermolide
Novartis



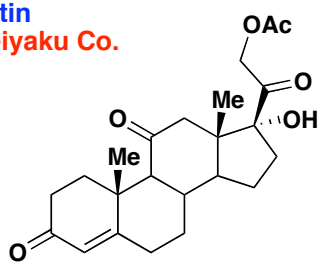
Ketorolac
Syntex



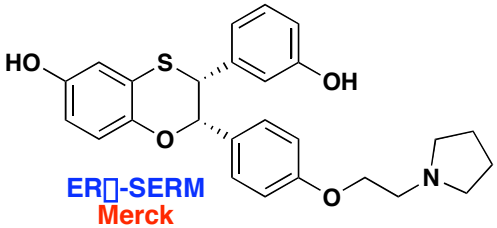
EGFR Irreversible Inhibitor
Pfizer



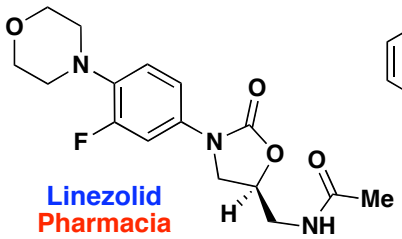
Biotin
Tanabe Seiyaku Co.



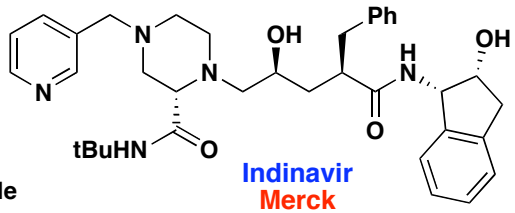
Cortisone
Merck



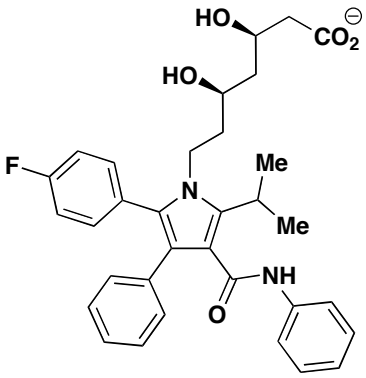
ER□-SERM
Merck



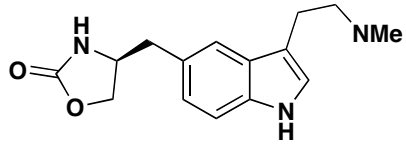
Linezolid
Pharmacia



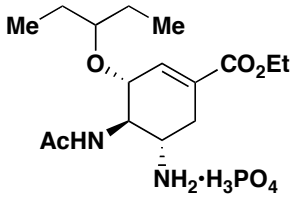
Indinavir
Merck



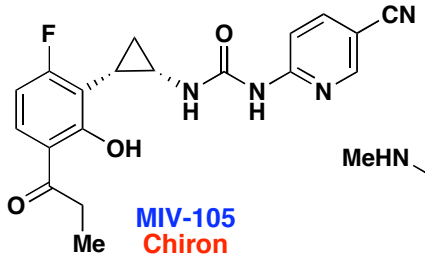
Lipitor
Pfizer



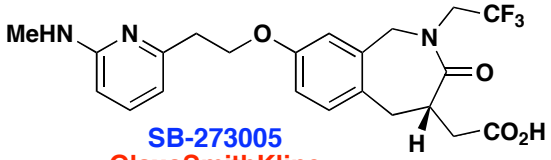
Zomig
AstraZeneca



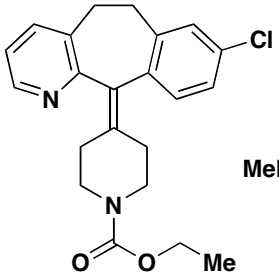
Tamiflu
Hoffmann-LaRoche



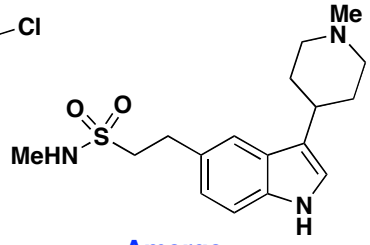
MIV-105
Chiron



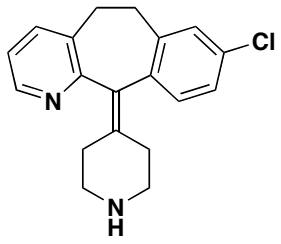
SB-273005
GlaxoSmithKline



Claritin
Schering-Plough



Amerge
GlaxoSmithKline



Clarinex
Schering-Plough

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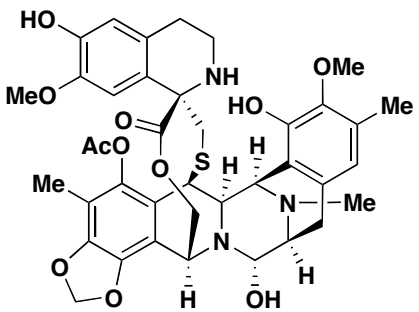
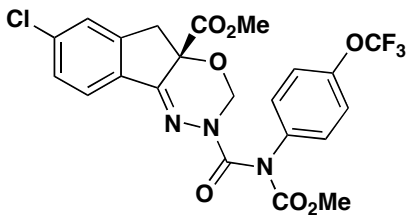
Masterpieces in Process Chemistry

11/3/04
Group Meeting

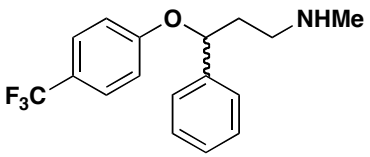
Selected Syntheses Not Discussed:



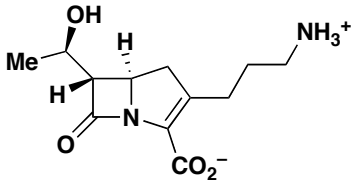
Ecteinascidin 743
Corey



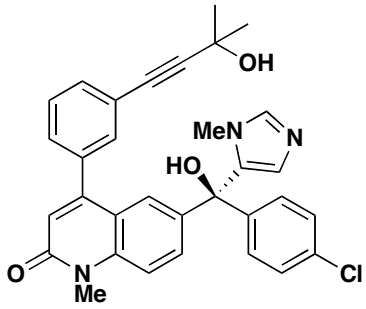
Indoxacarb
DuPont



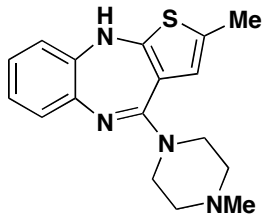
Prozac
Eli Lilly



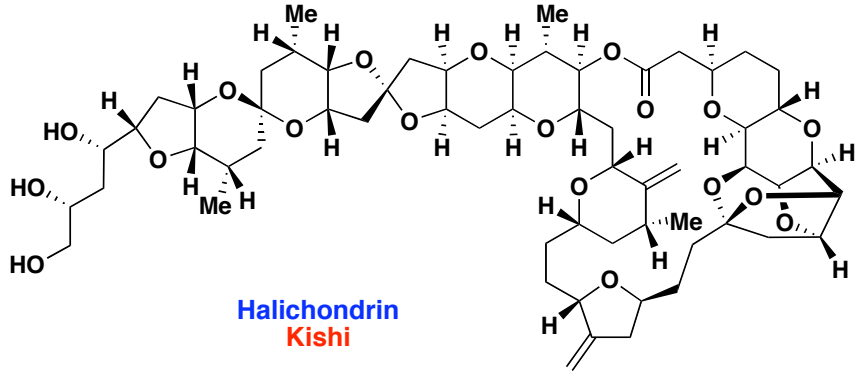
Thienamycin
Merck
See Jeremy Richter, Baran Group Meeting, January 2004



FTI Candidate
Pfizer



Zyprexa
Eli Lilly



Halichondrin
Kishi

Disclaimers:

1. This is by no means a comprehensive sampling of the many masterpieces in process chemistry.

2. Process syntheses are very difficult to locate and decipher, since most of the relevant literature is burried in patents and the words "process scale" do not appear in the titles.

3. Some of the syntheses not discussed above were not done so because they were either not actual process routes (Ecteinascidin 743, Halichondrin) or I was unable to locate the relevant literature in time.

4. To give this topic the credit it deserves would require the publication of *Classics in Process Chemistry*.

5. Many of the syntheses presented here are wonderfull full papers that delineate the entire conception process along with problems encountered along the way. I recommend these papers for more information.

Partial List of Transforms:
Zhao olefination, Parikh-Doering oxidation, Still-Genari olefination, Nozaki-Hiyama coupling, Evans-Saksena reduction, Kagan oxidation, Ullmann reaction, Strecker reaction, Moffit oxidation, Fukuyama coupling, Wohl-Zeigler bromination

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Masterpieces in Process Chemistry

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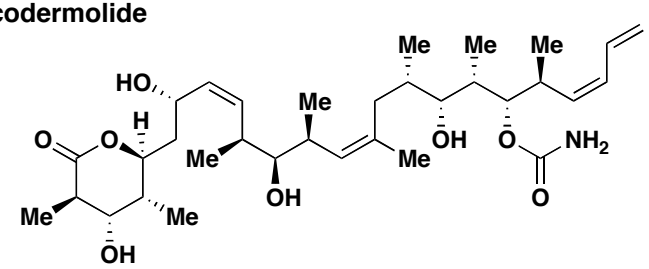
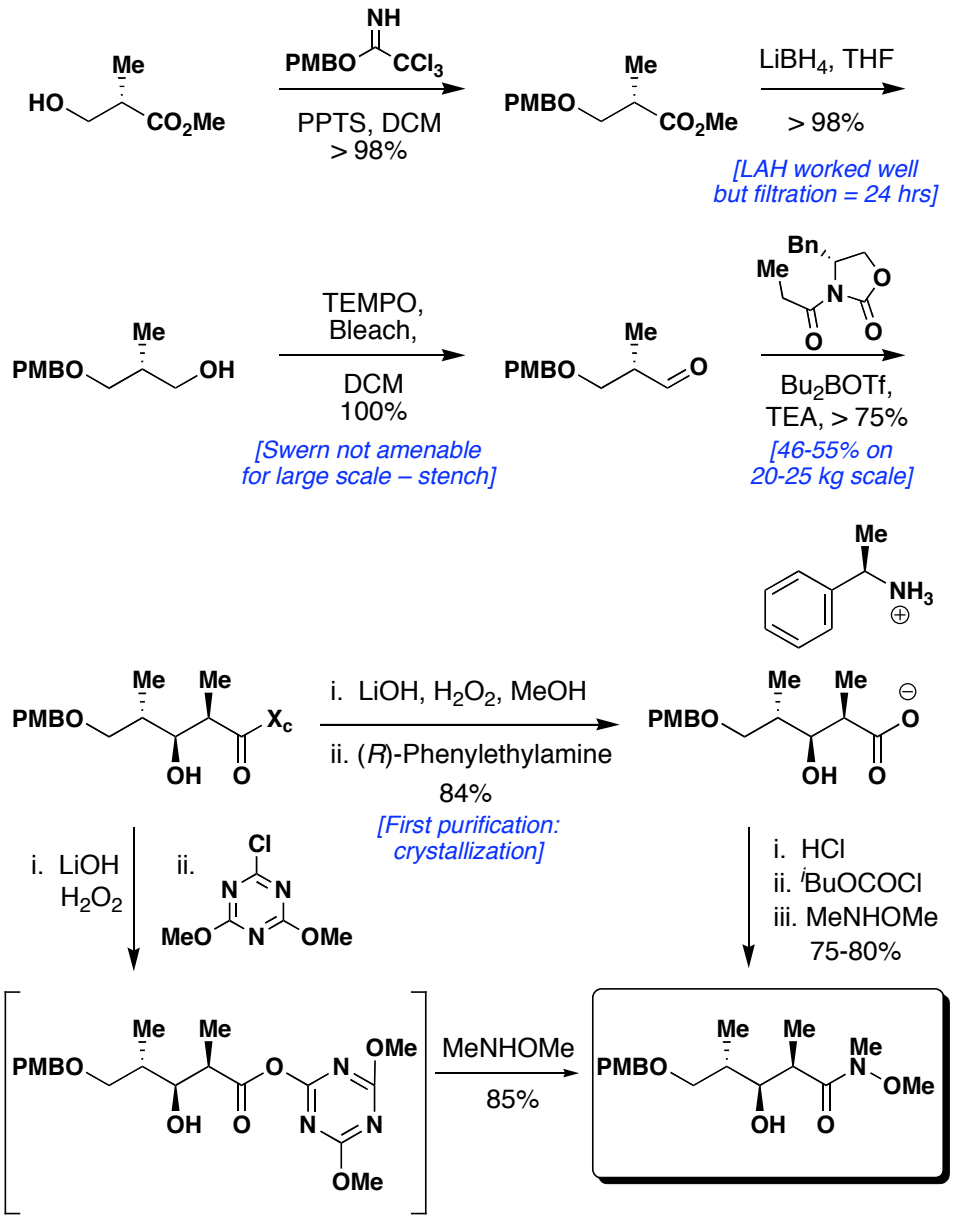
(–)-Discodermolide

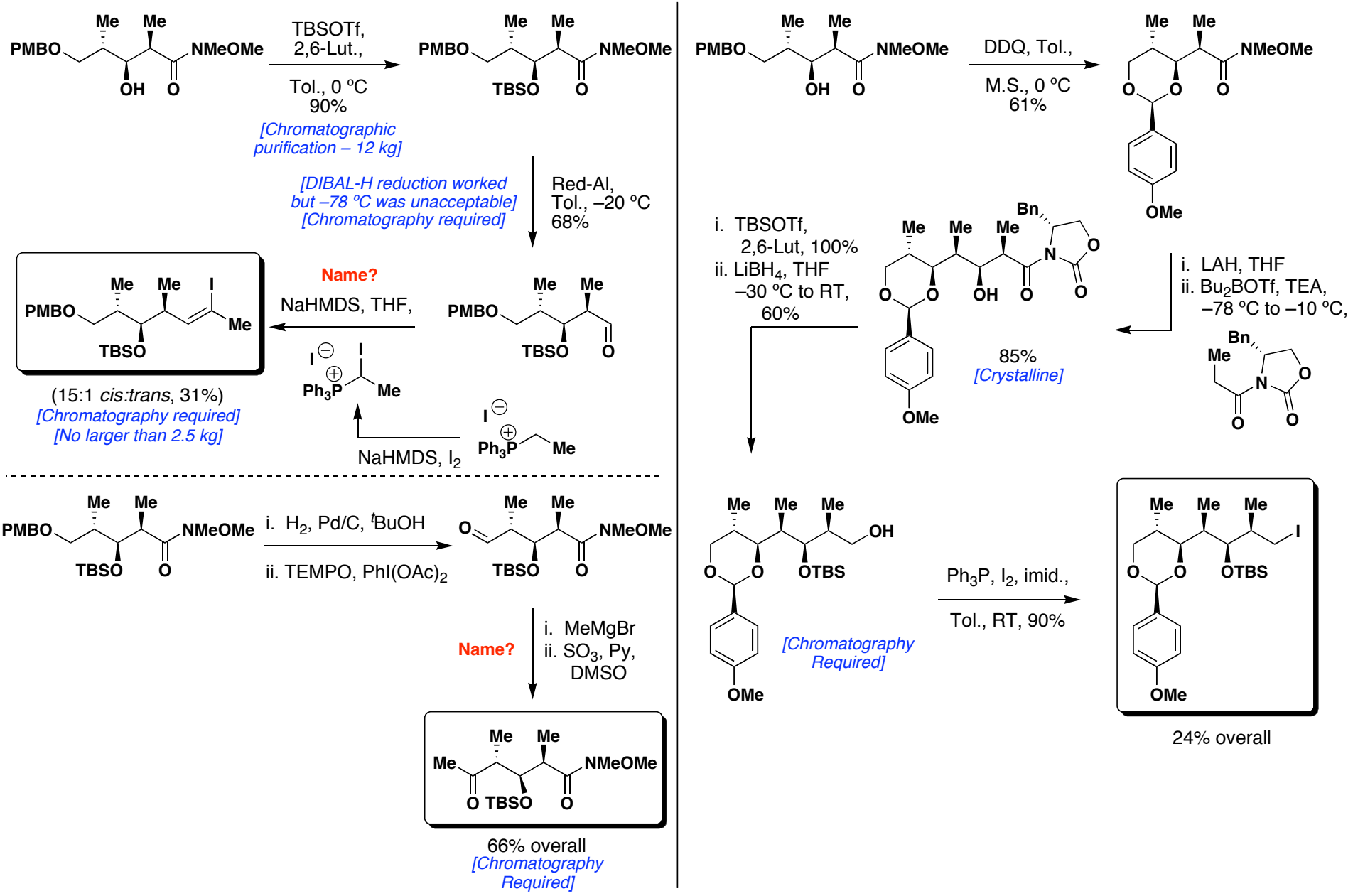


1. Non-taxane microtubule stabilizing agent (most potent known).
2. Small amounts available naturally and must be harvested by manned submersibles. Fermentation has not been successful so all material must come from total synthesis.
3. Currently in phase I clinical trials.
4. Previous syntheses:
   a. Schreiber, *JACS* **1993**, *115*, 12621; *ibid.* **1996**, *118*, 11054
   b. Smith, *JACS* **1995**, *117*, 12011; *OL* **1999**, *1*, 1823; *ibid.* **2000**, *2*, 1983; *JACS* **2000**, *122*, 8654
   c. Myles, *JOC* **1997**, *62*, 6098
   d. Marshall, *JOC* **1998**, *63*, 7885
   e. Paterson, *ACIEE* **2000**, *39*, 377; *TL* **2000**, *41*, 6935; *JACS* **2001**, *123*, 9535; *OL* **2003**, *5*, 35.
5. Novartis Process Synthesis:
   a. Drew heavily upon the Smith and Paterson approaches
   b. *OPRD* **2004**, *8*, 92-130

"One major problem associated with a synthesis of this length is the proper laboratory examination of the later reactions in a sequence. Initially, there are no answers to these supply problems; one just has to run the small-scale reaction and hope that on transfer to larger scale the reaction proceeds as expected. . . . On a positive note, this project was a first for Novartis, and its progress was avidly followed by the entire department who were all interested in the "disco". The success of this project and its chemistry paves the way for other, perhaps even more complex, natural products to be prepared for early-phase clinical evaluations and sends a positive message to both the isolation and synthetic academic community and possibly other pharmaceutical companies that: "your work need not just be of academic interest" and it may be worth taking a few risks. A total of 43 chemists participated in the concept of the synthesis, experimental design, and execution. . . . The hybridized Novartis–Smith–Paterson synthetic route that resulted in the preparation of 60 g of a structurally complex molecule containing 13 stereogenic centers is a crowning achievement to all those who participated in this endeavor. The option of optimizing the present synthesis further or replacing with a better one is a topic of our ongoing studies, and we are confident of climbing this mountain as the situation demands."



Masterpieces in Process Chemistry



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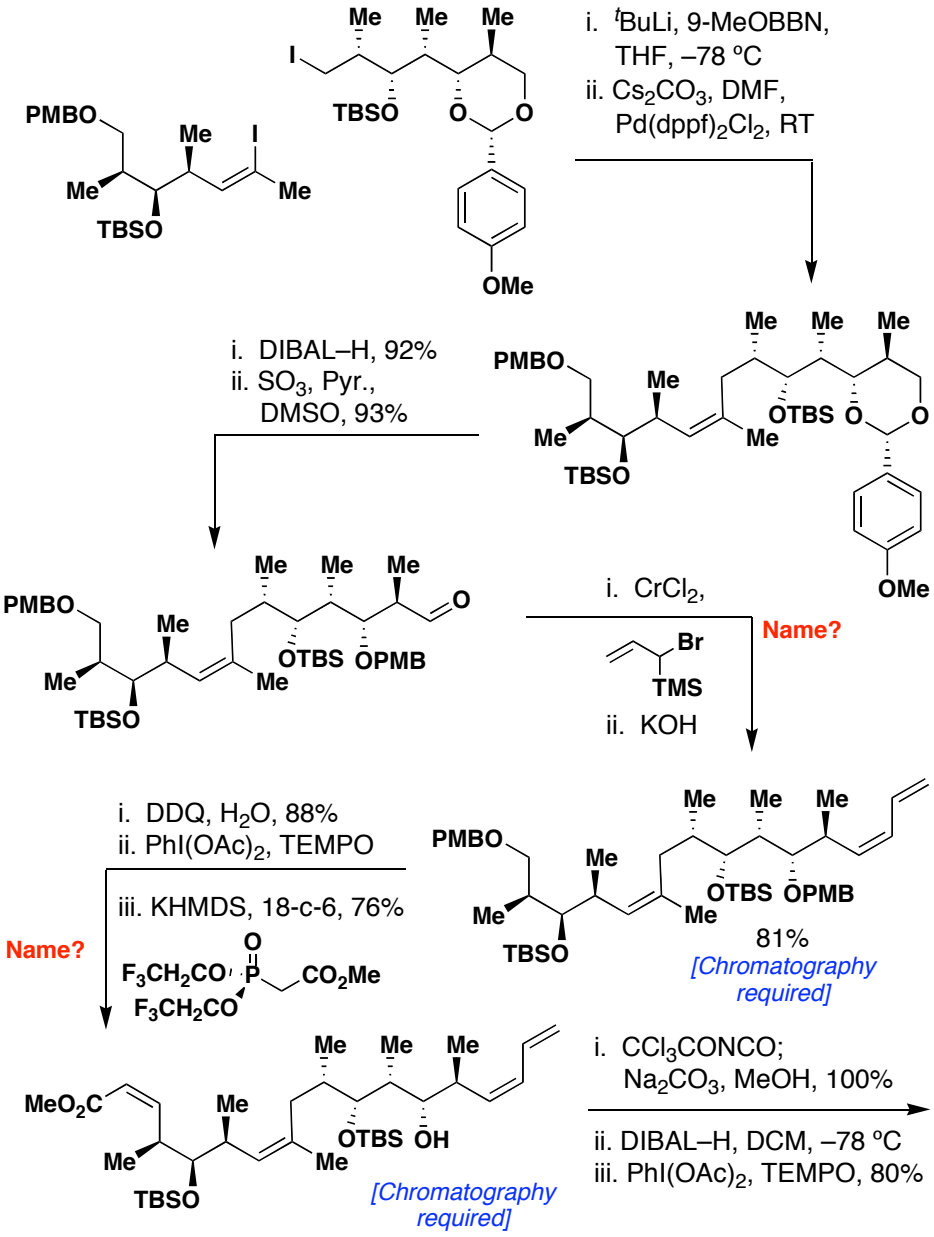
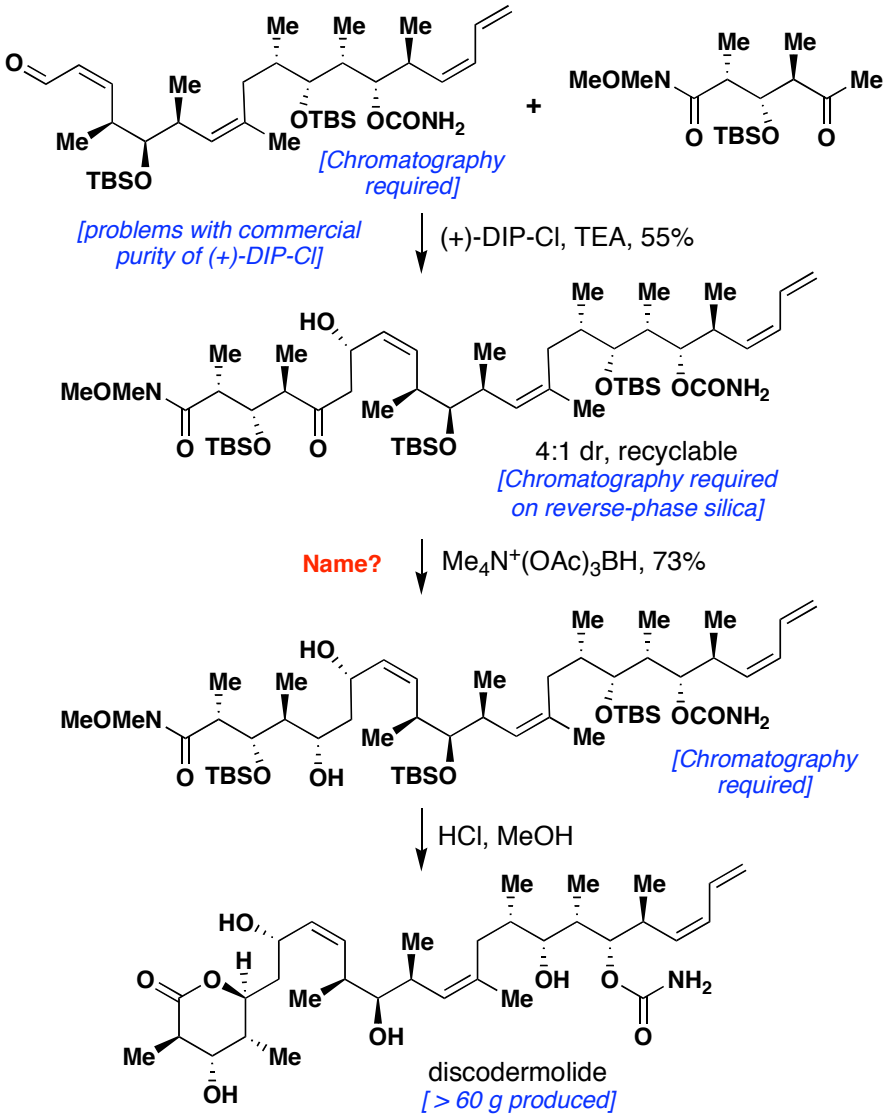
Masterpieces in Process Chemistry

11/3/04
Group Meeting





39 steps, 17 chromatographic purifications, 20 months
7 problematic steps identified and being optimized

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Masterpieces in Process Chemistry

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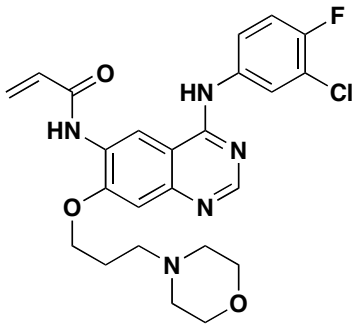
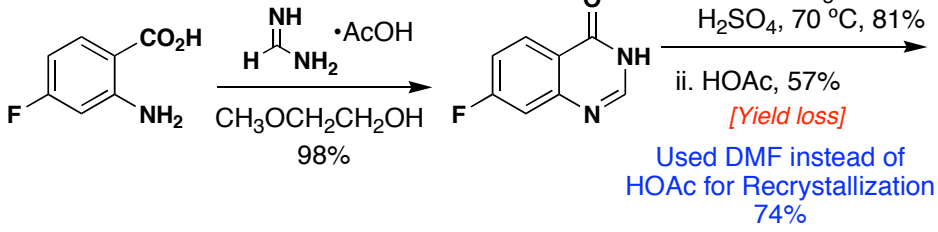
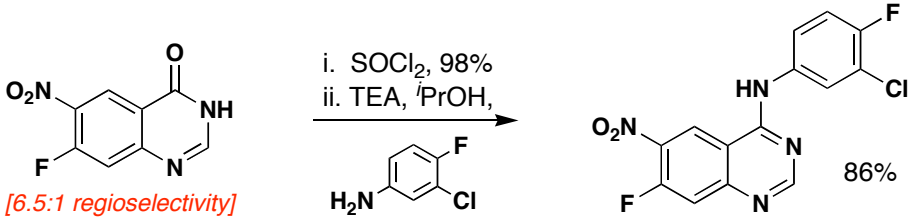
EGFR Irreversible Inhibitor



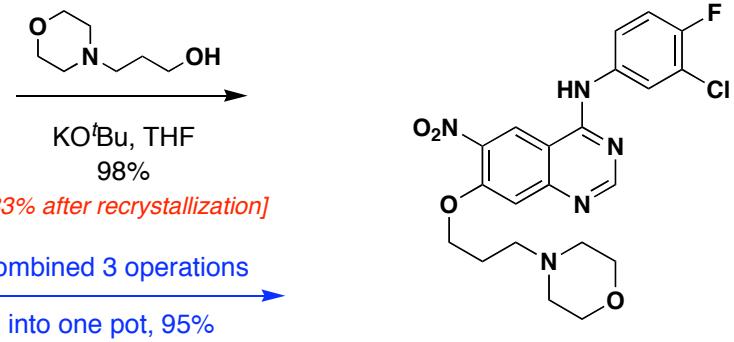
1. Treatment of solid tumors.
2. Inhibits Epidermal Growth Factor Tyrosine Kinase.
3. Process synthesis – Rober Hughes, Pfizer, Gordon Research Conference Presentation.

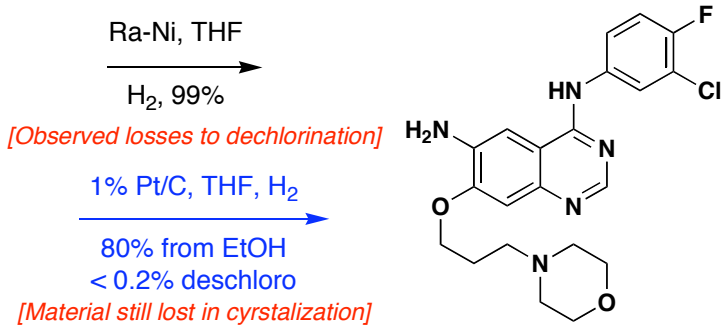
Initial Route **Problems** **Improved Route**

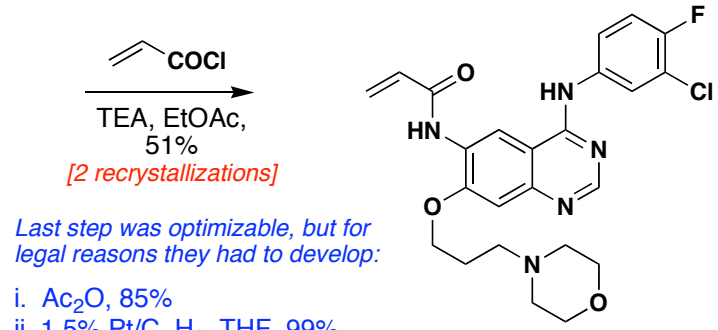




Could not improve



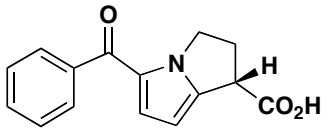




Final:
8 steps (3 pots)
55% overall yield
produced multikilo's

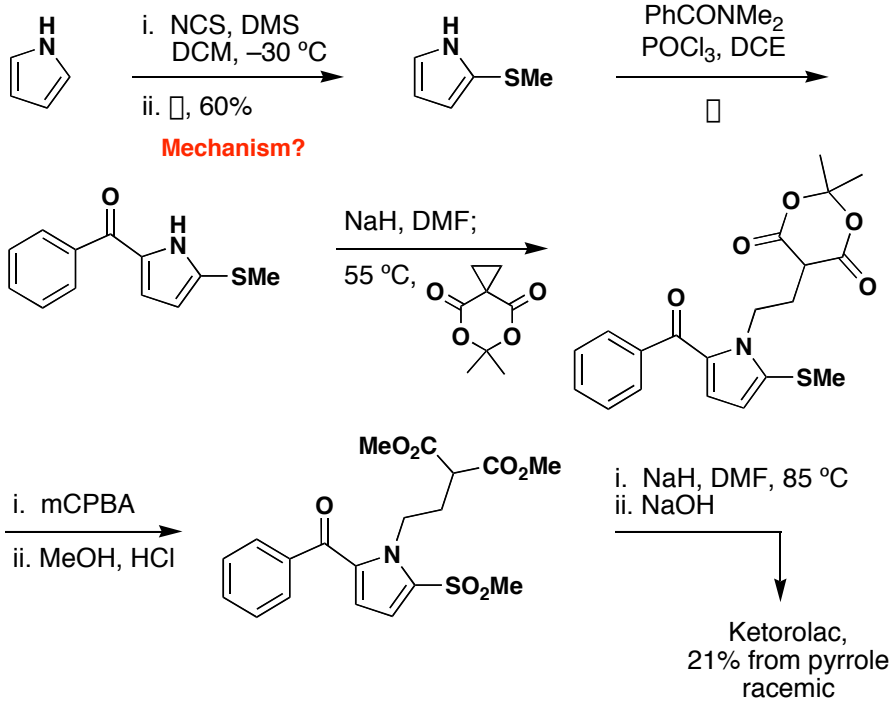
Masterpieces in Process Chemistry

Ketorolac

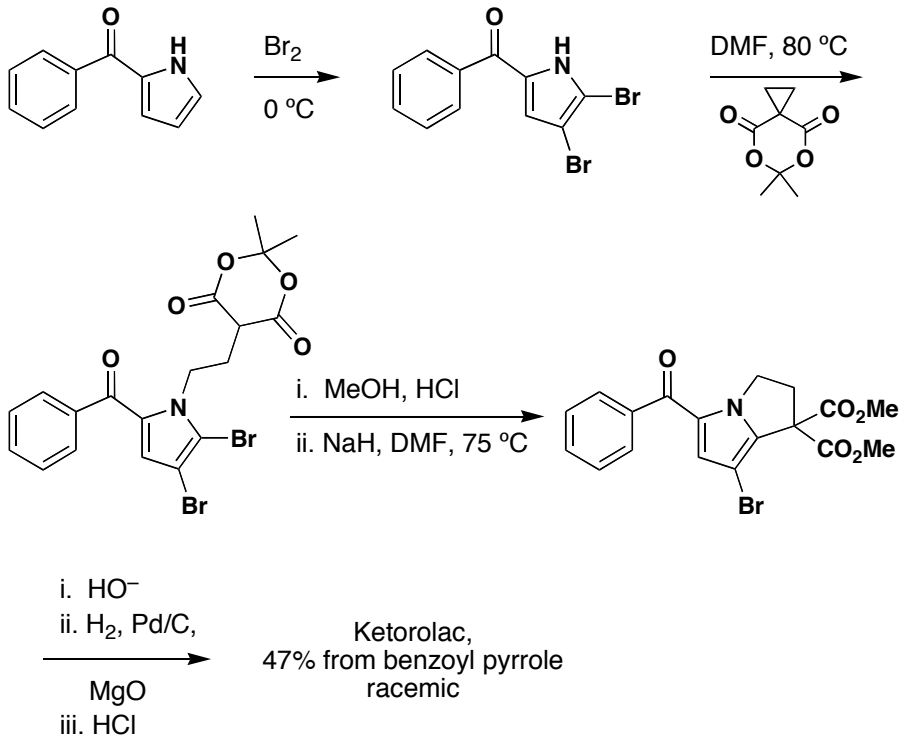


1. Non-steroidal antiinflammatory drug (NSAID).
2. Powerful antiinflammatory and analgesic activity.
3. 10 mg equiefficacious with morphine (10 mg) for post-operative pain.
4. 10 mg equiefficacious with aspirin (650 mg) for postpartumpain.
5. 10 mg equiefficacious with acetaminophen (1 g) or acetominophen (600 mg)/codein (60 mg) combination.
6. Syntex development: Muchowski, *Adv. Med. Chem.* **1992**, *1*, 109.

1st Generation Route



2nd Generation Route



3rd Generation Route

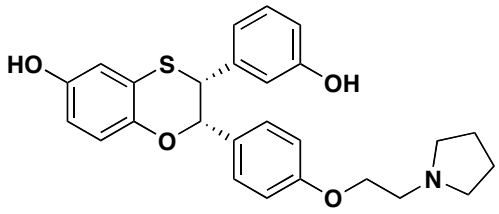
Begins from Pyrrole and proceeds in 45% overall yield:
See US Patent 6,197,976

New Chemistry Discovered:

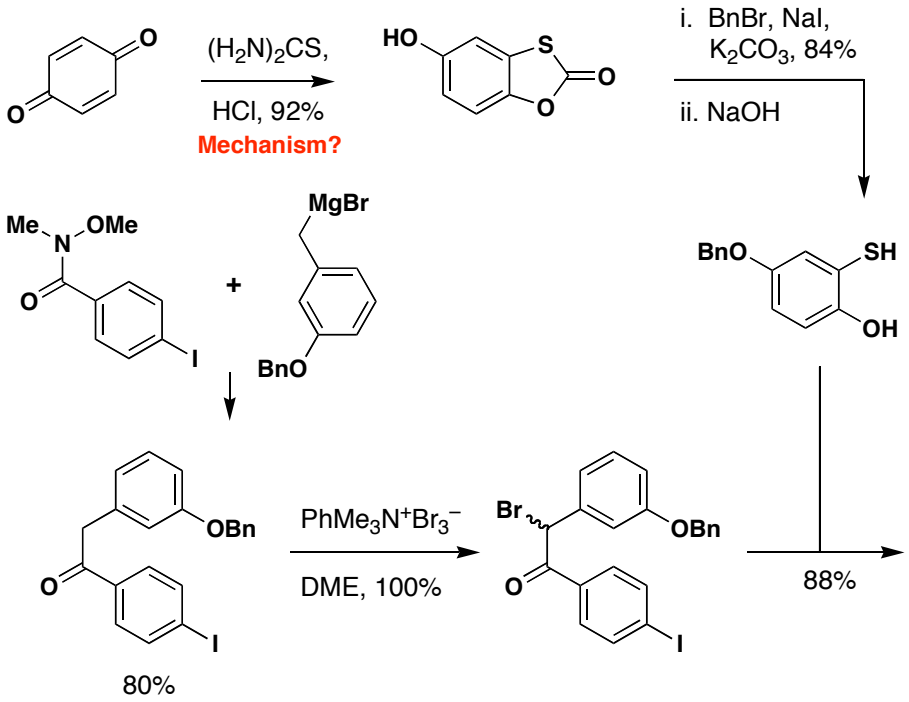
1. Selective substitution of pyrrole at C–3 when protected as *N*–Silyl.
2. Acid induced isomerization of C–2 substituted pyrroles to C–3.
3. New routes to pyrrole-2-carboxaldehydes.
4. New routes to acylpyrroles.
5. Mild reduction of acylpyrroles to alkylpyrroles.
6. Conversion of acylpyrroles to acylpyrrolidines.
7. First reported intramolecular carbenoid addition to a pyrrole nucleus.

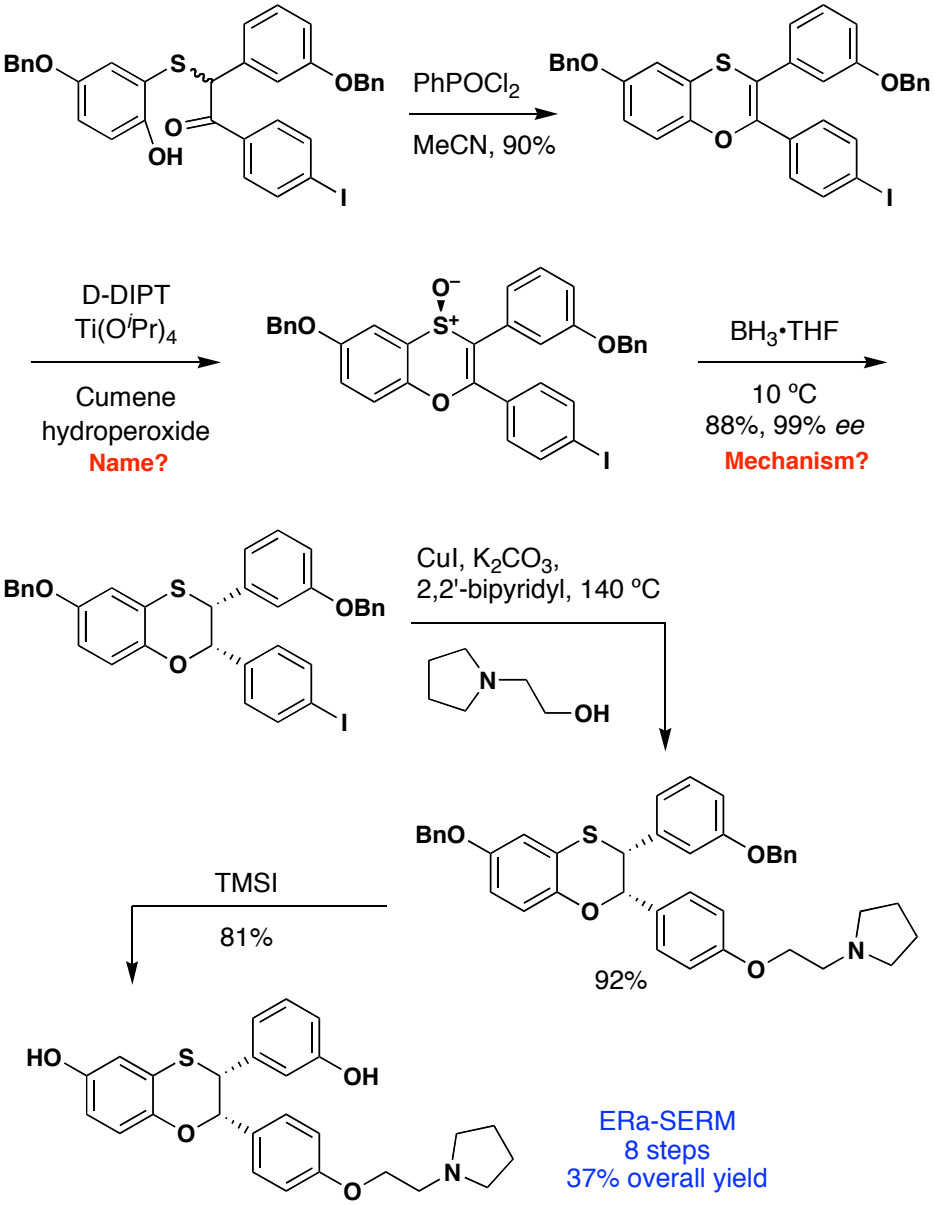
Masterpieces in Process Chemistry

ERα-SERM



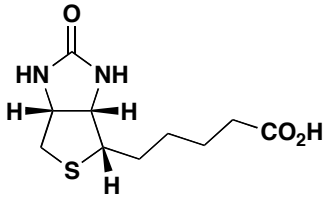
1. SERM = selective estrogen receptor modulator.
2. Potentially useful for the treatment of bone loss, cartilage degeneration, endometriosis, uterine fibroid disease, hot flashes, increased levels of low-density lipoprotein cholesterol, cardiovascular disease, obesity, incontinence and cancer.
3. Synthesis: Merck, *PNAS*, **2004**, *101*, 5776.



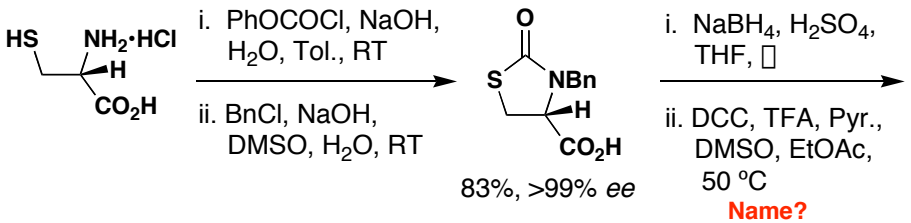


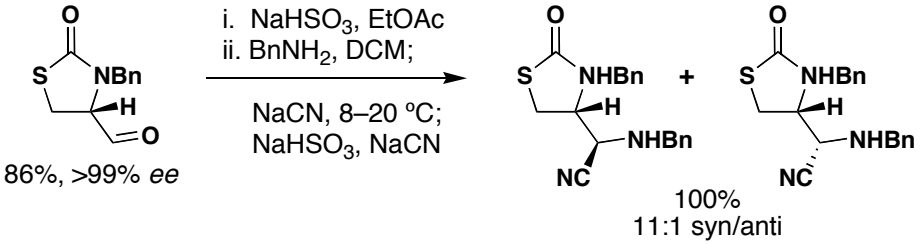
Masterpieces in Process Chemistry

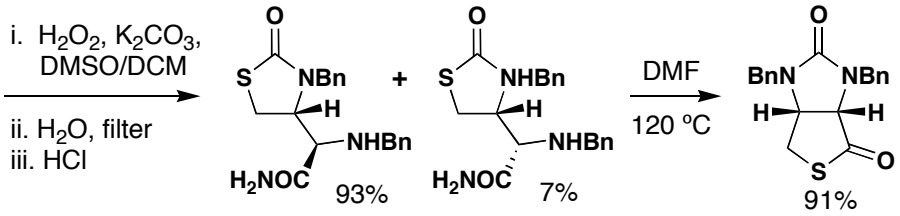
Biotin

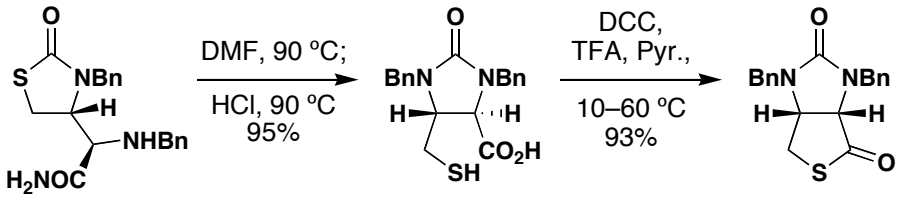


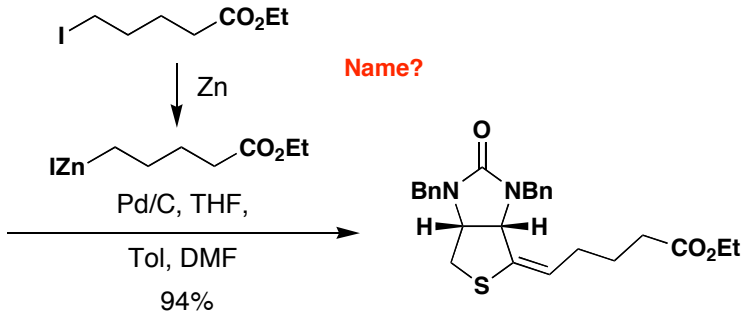
1. Important in human nutrition and animal health.
2. > 80 tons produced synthetically anually.
3. Synthesis: Tanabe Seiyaku Co., *Chem. Eur. J.* **2004**, ASAP.
4. For a comprehensive review of Biotin syntheses see:
   Ryan Shenvi, Baran Lab Group Meeting, July 2003.

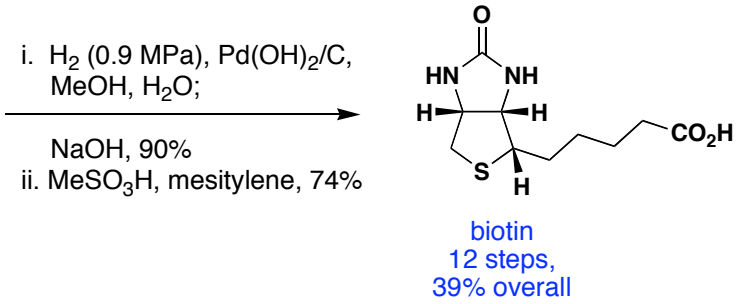






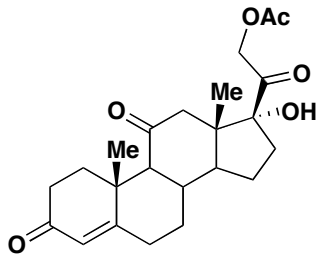




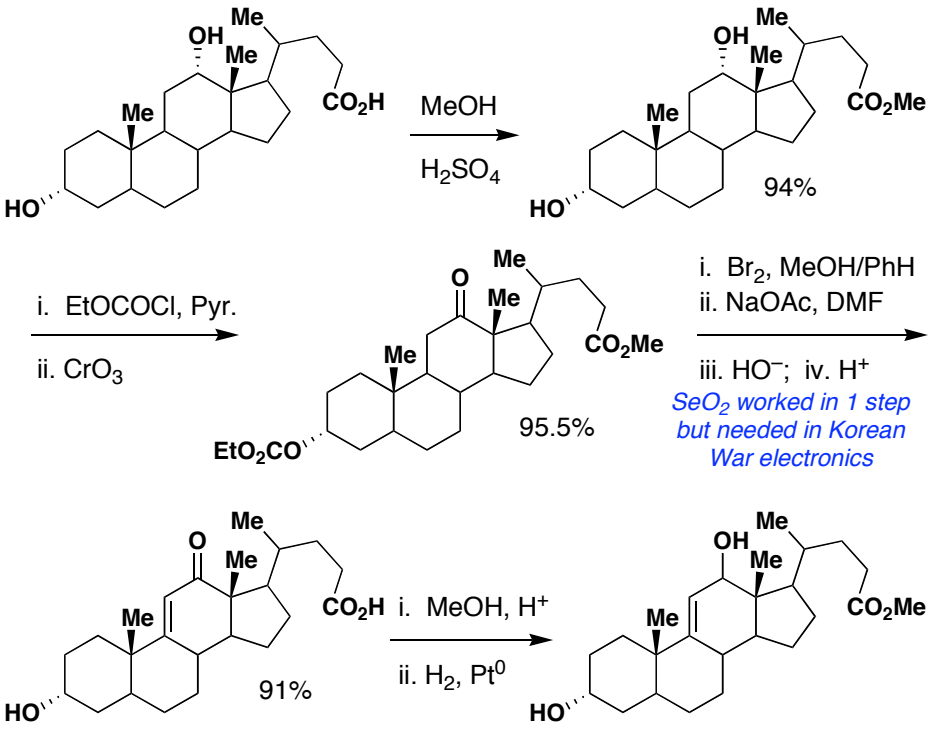


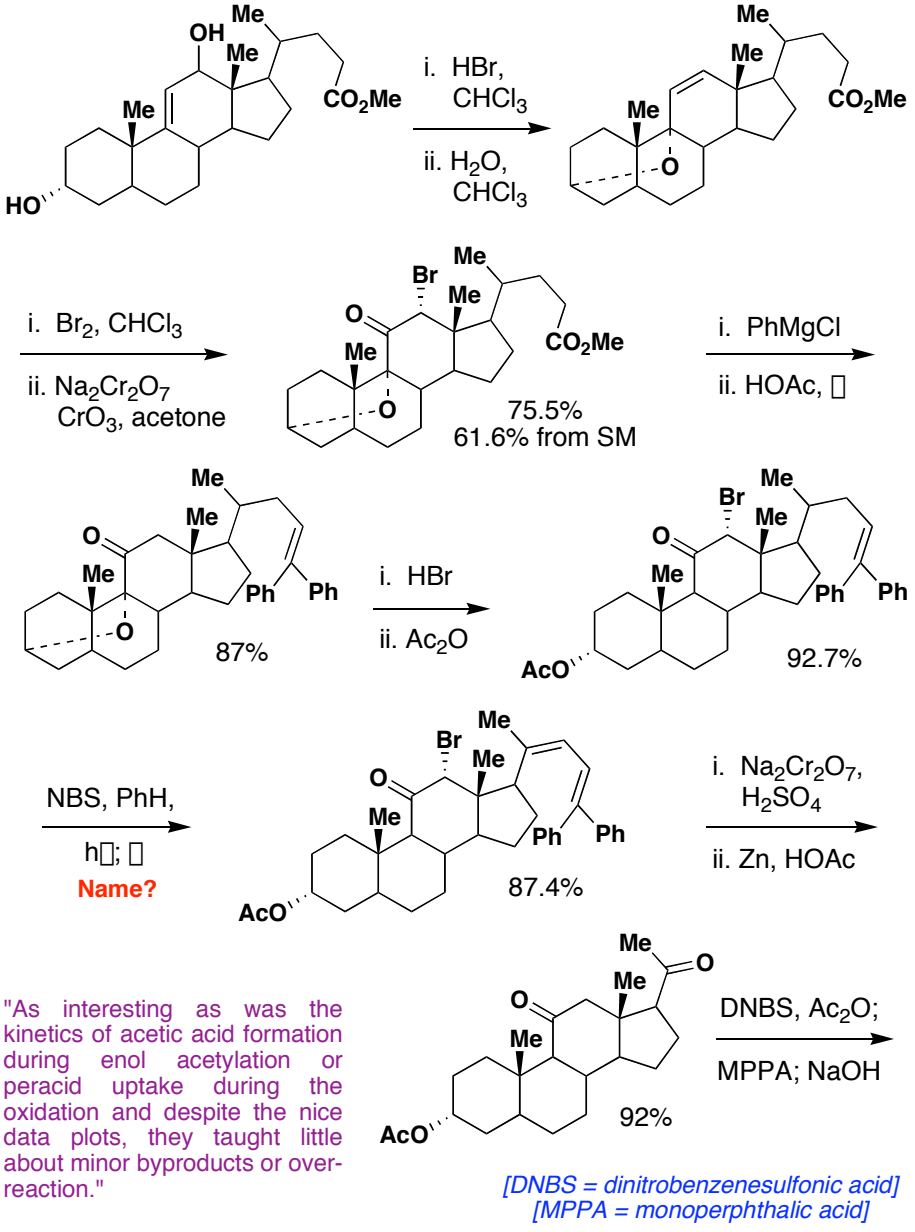
Masterpieces in Process Chemistry

Cortisone



1. Synthesis at the time was meant to provide large quantities to test.
2. Starting material readily available from cow bile.
3. Work done in the early 1950's without modern spectroscopy.
4. Work done in less than 2 years.
5. Process synthesis: Merck, *OPRD*, **2004**, *8*, 708.

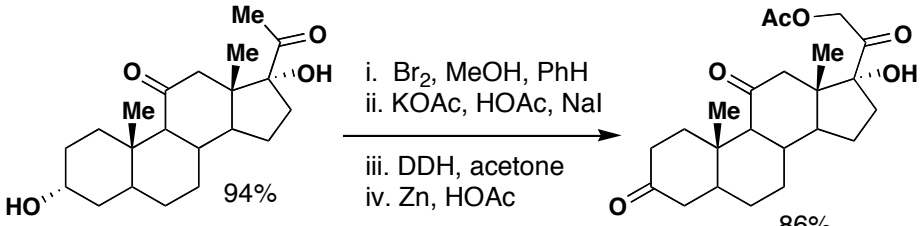




"As interesting as was the kinetics of acetic acid formation during enol acetylation or peracid uptake during the oxidation and despite the nice data plots, they taught little about minor byproducts or over-reaction."

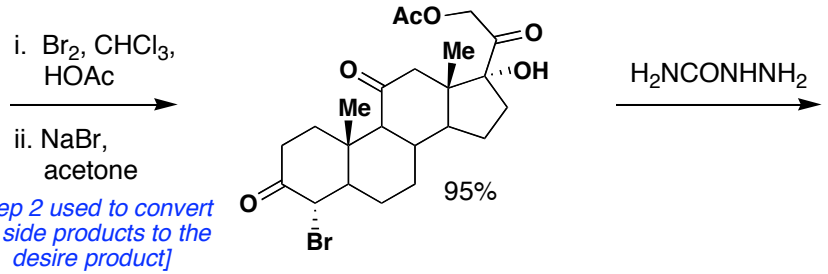
[DNBS = dinitrobenzenesulfonic acid]
[MPPA = monoperphthalic acid]

Masterpieces in Process Chemistry



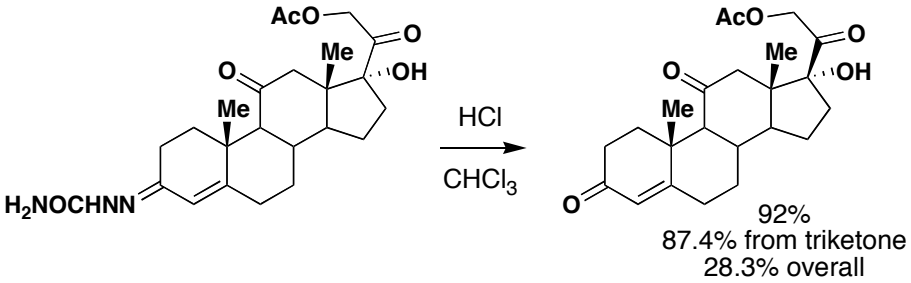
[DDH = dibromodimethylhydantoin]

"With benzene, we actually considered it beneficent in that carbon tetrachloride was a known liver toxin. Little did we know at the time that we were exchanging it for what would many years later be labeled a carcinogen!"



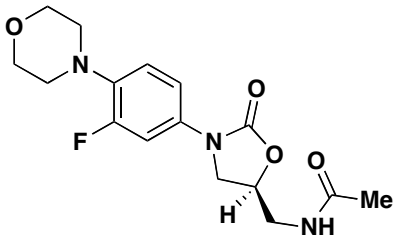
[step 2 used to convert all side products to the desire product]

"A great deal of development was still required as the demonstration with an incompletely developed process was initiated in the new plant. Some improvements were made on an ad-hoc basis, at times prematurely, with production at sub-optimal performance better than no production at all. For better and for worse, such a modus operandi is no longer practiced, courtesy of FDA and cGMP regulations."

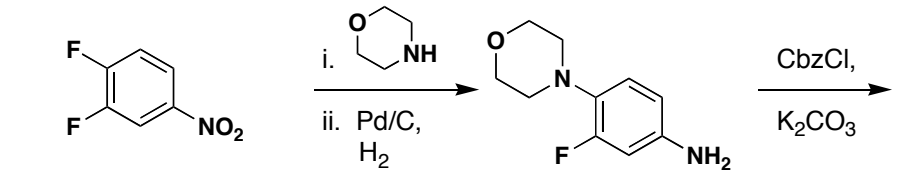


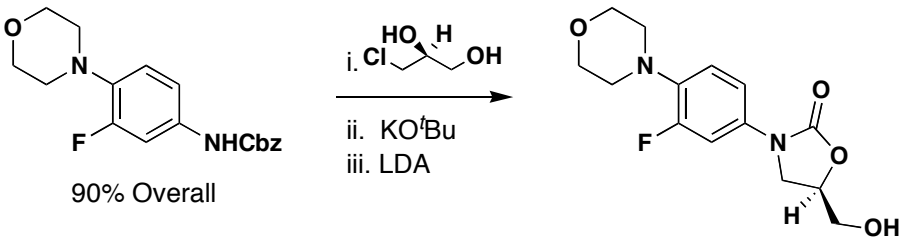
"Product elegance has long been an ethereal objective of ethical pharmaceutical companies; it is sometimes an expensive one. Planning for the last step has to include concerns of color and appearance as well as chemical purity. It is annoying to some synthetic chemists to see a difficultly won, elegant, white crystalline material subjected by pharmacists to granulation, sometimes coloration, and compression to an unnatural form."

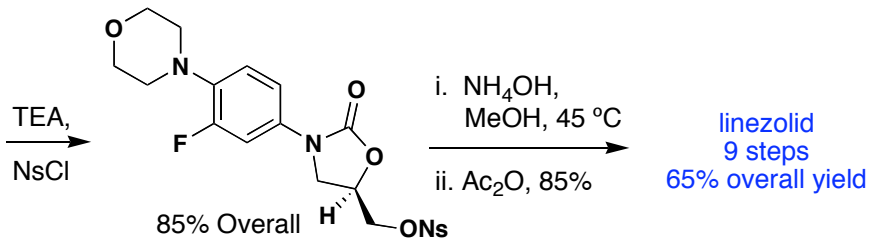
Linezolid



1. Active against gram-positive and gram-negative bacteria with potency in the 2-4 □g/mL.
2. Synthesis: Pharmacia/Pfizer, *ACIEE*, **2003**, *42*, 2010, US Patent: 5837870.



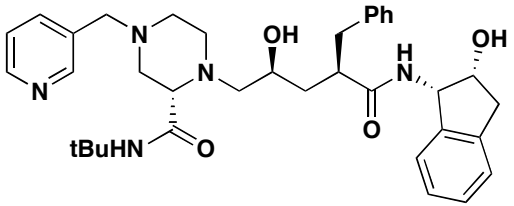




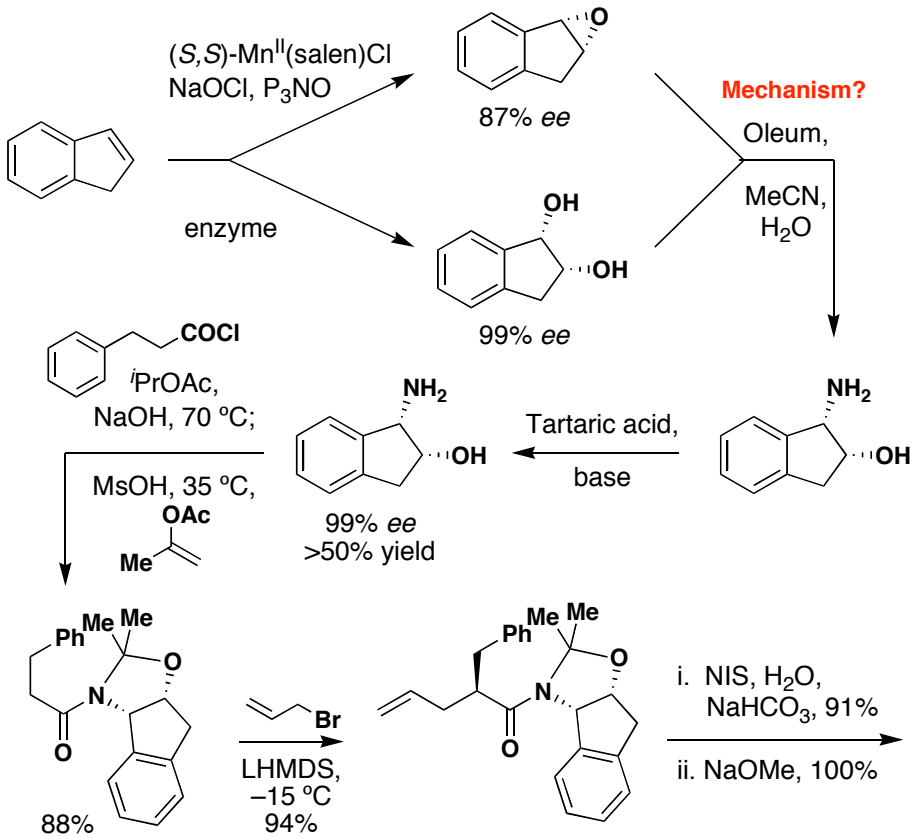
linezolid
9 steps
65% overall yield

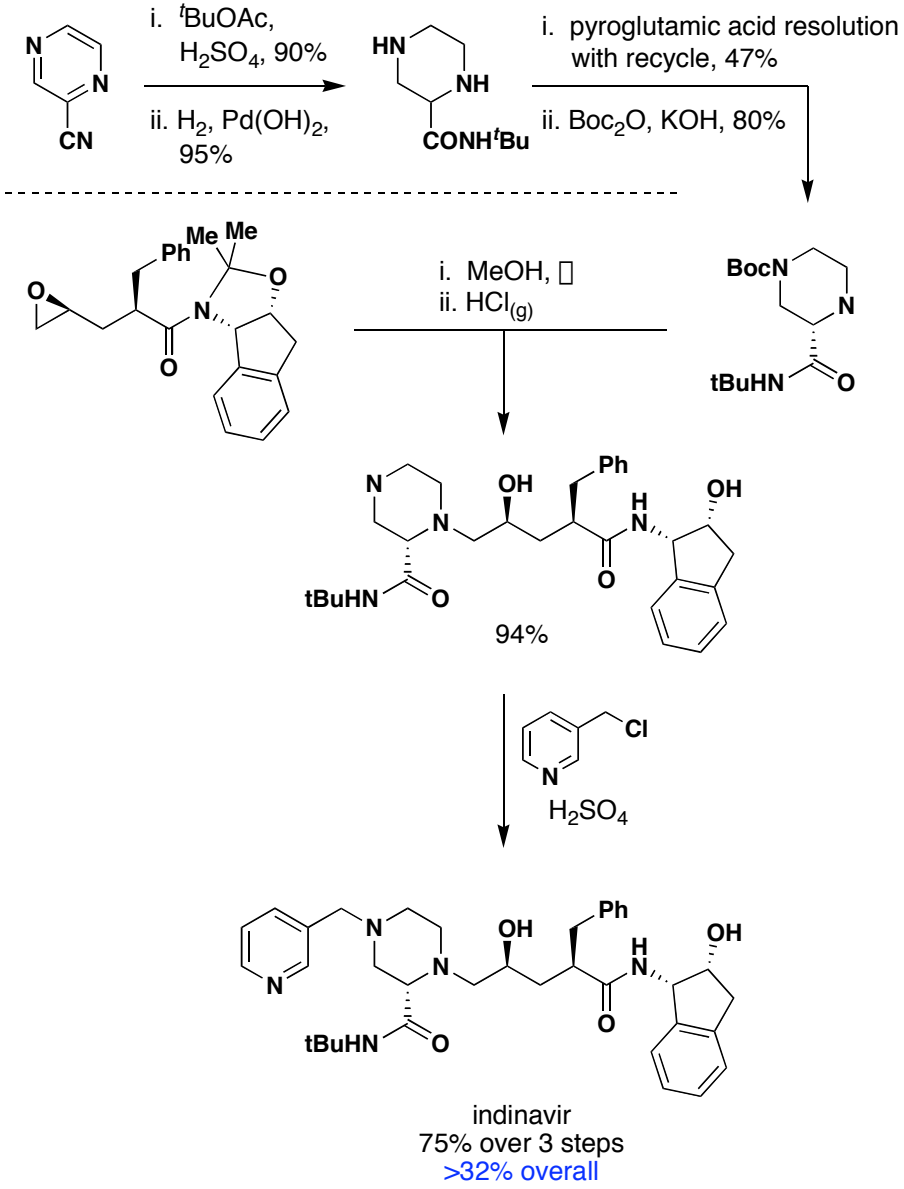
Masterpieces in Process Chemistry

Indinavir



1. HIV Protease Inhibitor.
2. Synthesis: Merck, *Chimia*, **1997**, *51*, 306.
   Narendra Ambhaikar, Baran Group Meeting, July 2004.



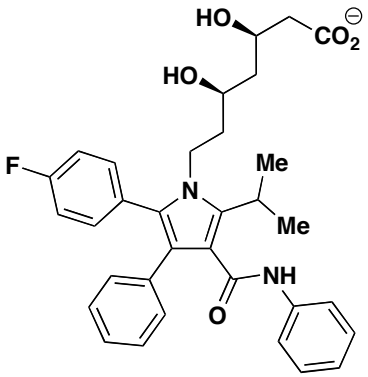


Richter

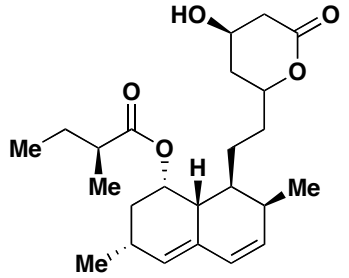
Masterpieces in Process Chemistry

11/3/04
Group Meeting

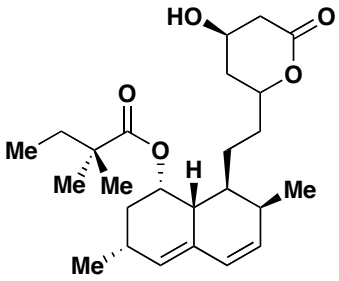
Lipitor



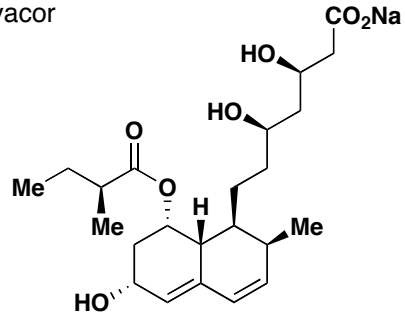
1. Hypolipidemic.
2. Number one selling drug of all time (Natural product inspired).
3. Synthesis: Bruce Roth, Pfizer, *Prog. Med. Chem.* **2002**, *40*, 1.
4. Largest competitors:



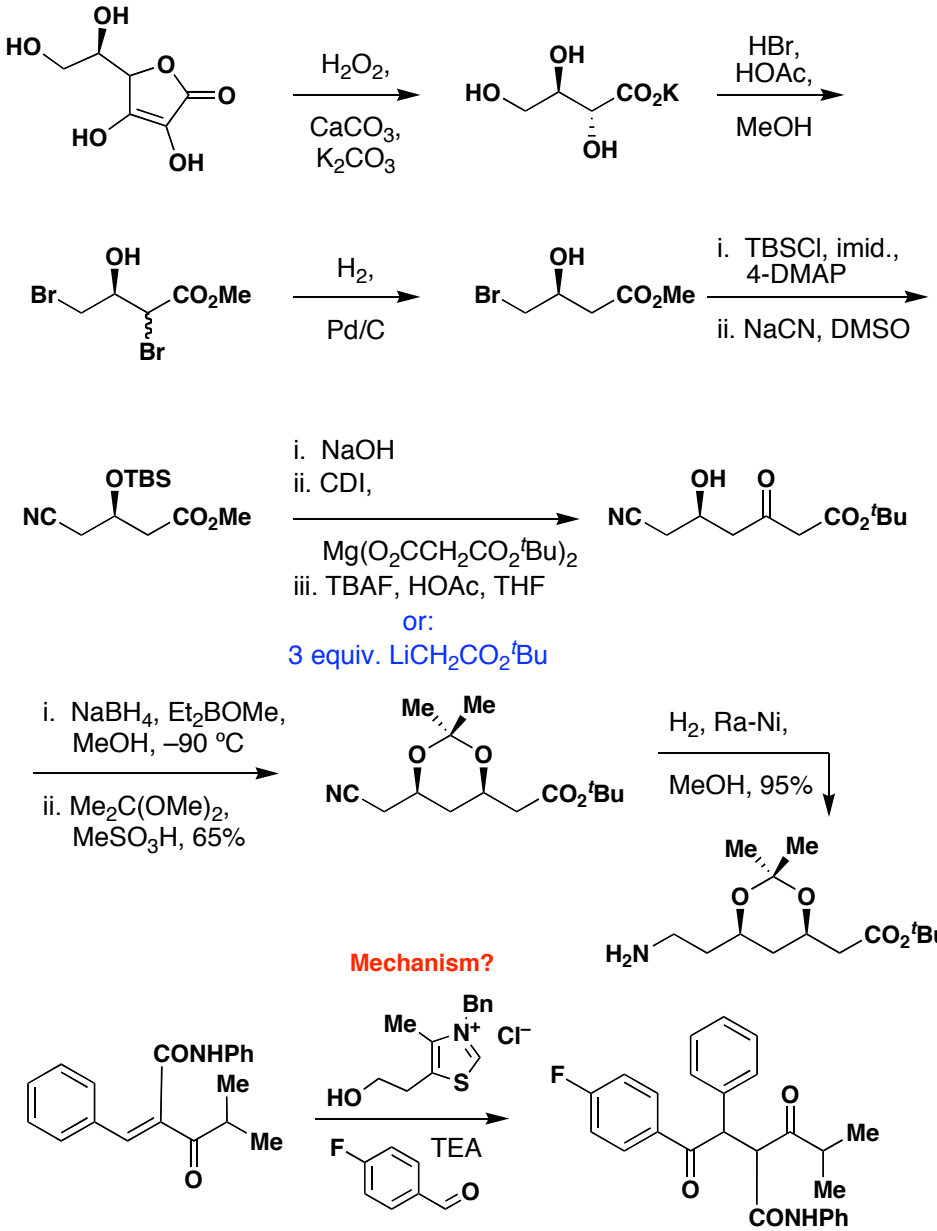
Mevacor



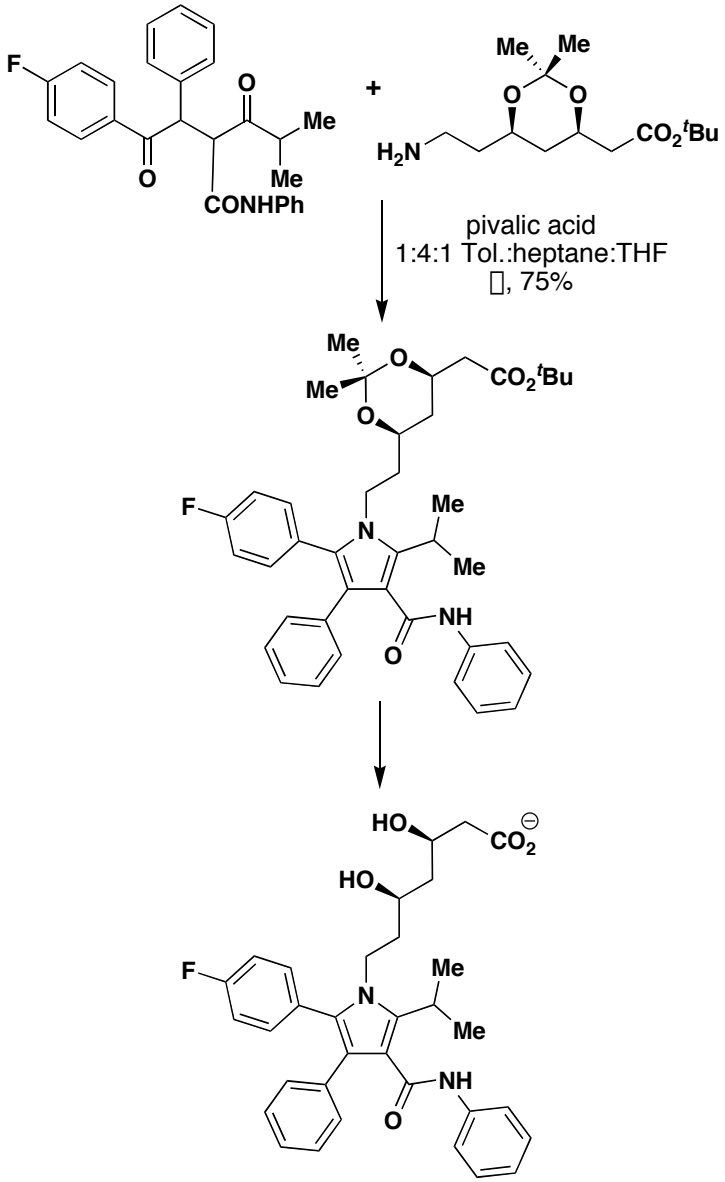
Zocor



Pravacol

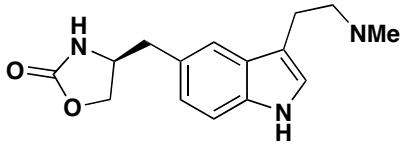


Masterpieces in Process Chemistry

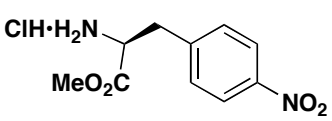


"...produced stereochemically pure atorvastatin calcium in a convergent, commercially viable manner which accomplished the original vision for the synthesis developed in discovery chemistry, but was reduced to practice in chemical development."

Zomig

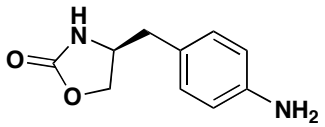


1. Used to treat migraine headaches.
2. Synthesis: AstraZeneca, US Patent 6084103, 6160123, Li, J.J. *Contemporary Drug Synthesis*, Wiley, **2004**.



i. Na_2CO_3, H_2O, EtOAc; $ClCO_2Bu$
ii. H_2, 5% Pd/C, EtOAc, BuOH, 30–50 °C

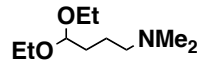
iii. $NaBH_4$, BuOH, 35 °C
iv. NaOMe, MeOH, BuOH, 85 °C



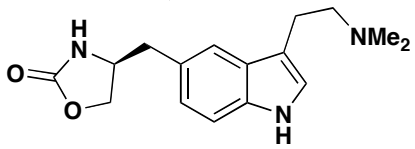
precipitated upon cooling

i. $NaNO_2$, HCl, 0 °C
ii. Na_2SO_3, H_2O, 0–60 °C

iii. reflux, 3 hr



iv. 10% EtOH/EtOAc



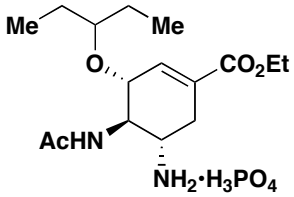
No yields given
One-pot procedure

Richter

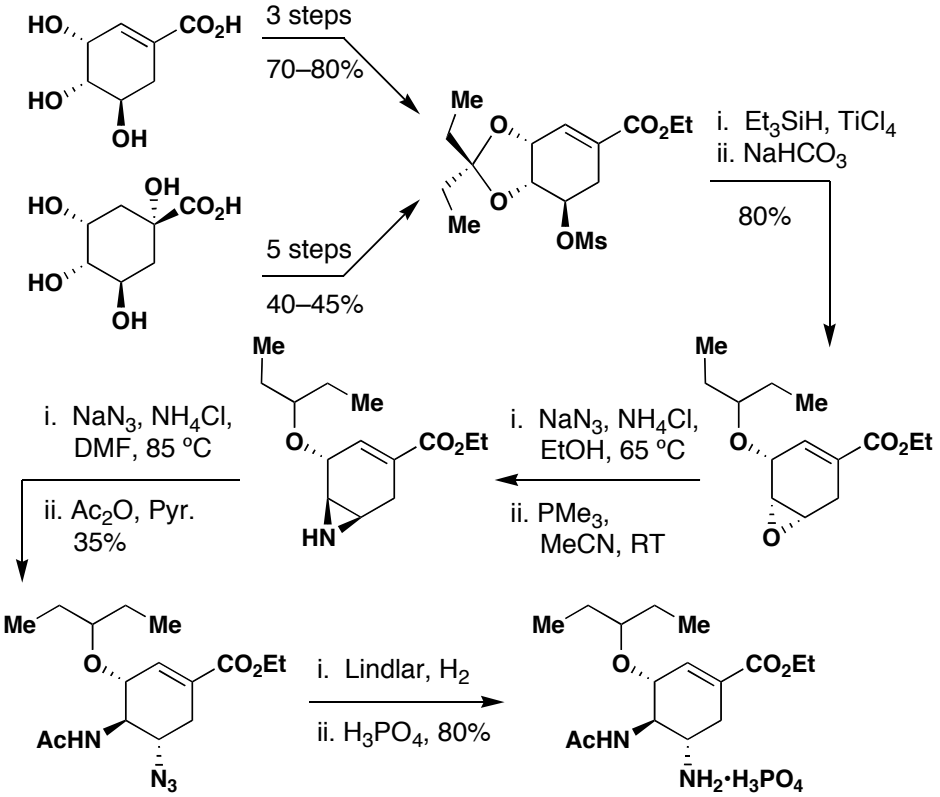
Masterpieces in Process Chemistry

11/3/04
Group Meeting

Tamiflu



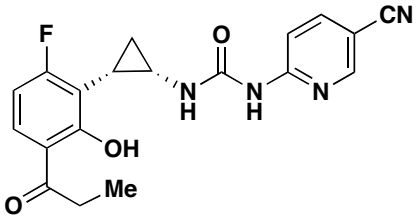
1. Potent inhibitor of influenza neuraminidase at nanomolar concentrations.
2. Synthesis: Hoffmann-LaRoche, *Chimia*, **2004**, *58*, 621.



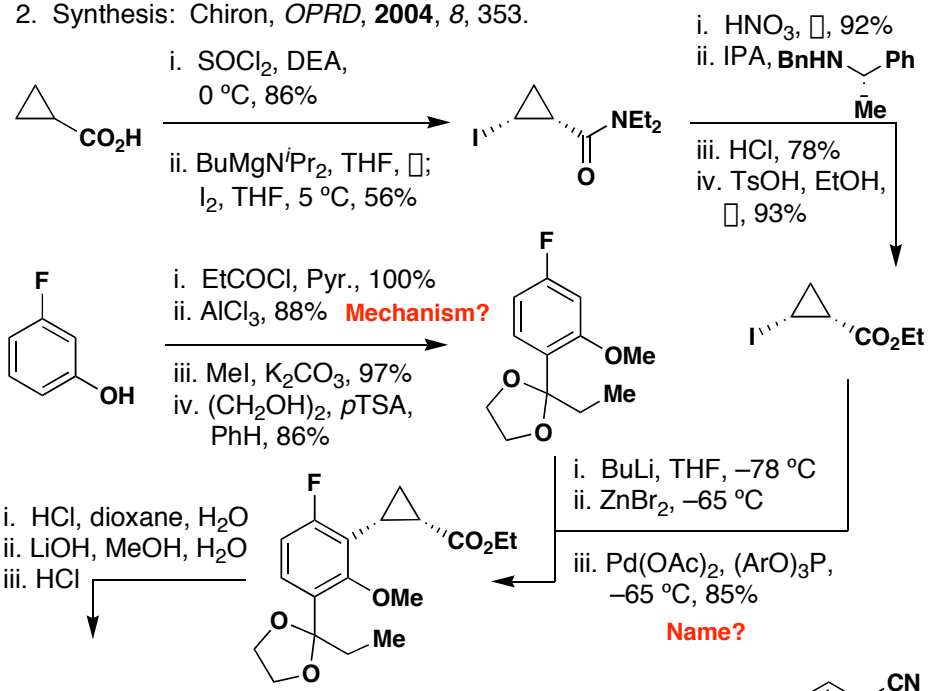
[A series of studies was undertaken to improve the efficiency and safety of this route, through the replacement of the azide chemistry, as well as beginning with more cost effective starting materials.]

Tamiflu
35% from Shikimic acid
20% from Quinic acid

MIV-105



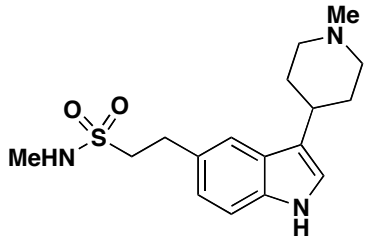
1. Non-nucleoside reverse transcriptase inhibitor.
2. Synthesis: Chiron, *OPRD*, **2004**, *8*, 353.



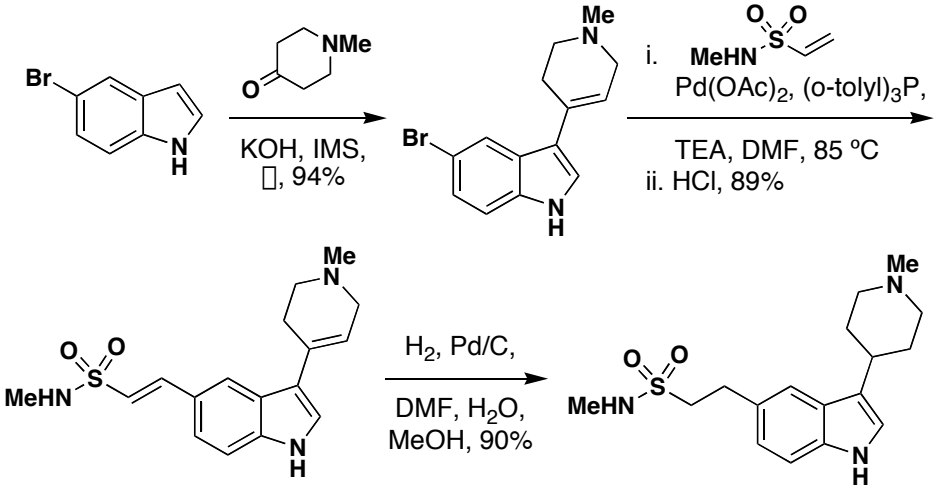
MIV-105
27% overall yield

Masterpieces in Process Chemistry

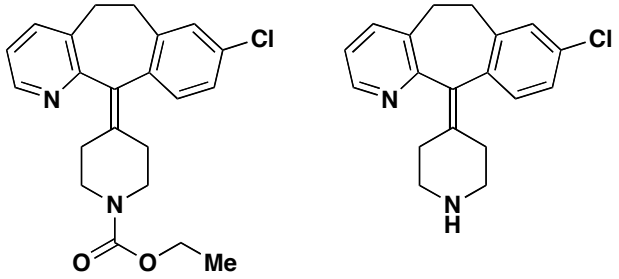
Amerge



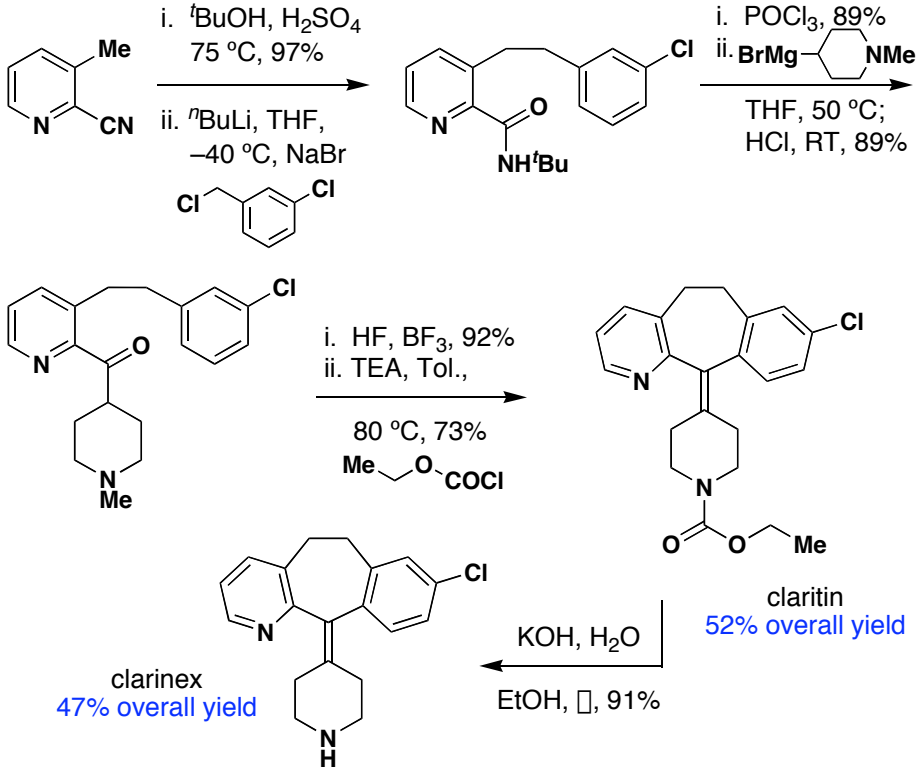
1. Used to treat migraine headaches.
2. Synthesis: GlaxoSmithKline, *J. Med. Chem.* **1995**, *38*, 3566,
   Li, J.J. *Contemporary Drug Synthesis*, Wiley, **2004**.



Claritin and Clarinex

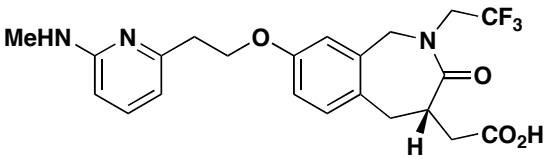


1. Antihistamines.
2. Synthesis: Schering-Plough, *J. Org Chem.* **1989**, *54*, 2242,
   Li, J.J. *Contemporary Drug Synthesis*, Wiley, **2004**.

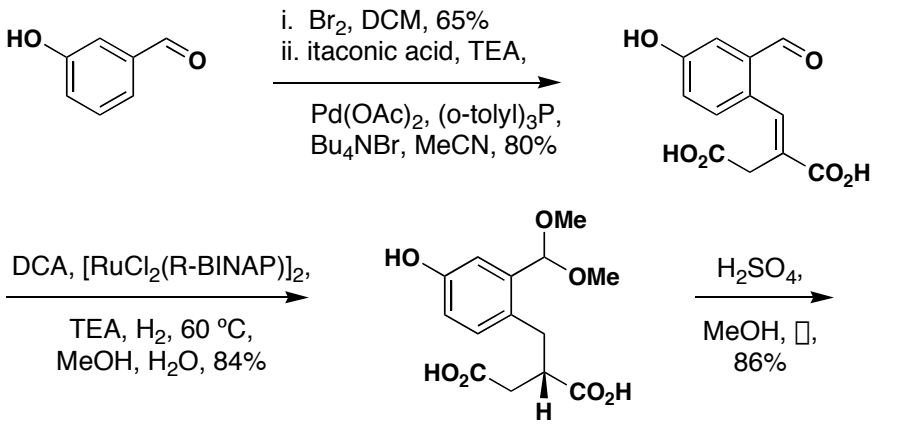


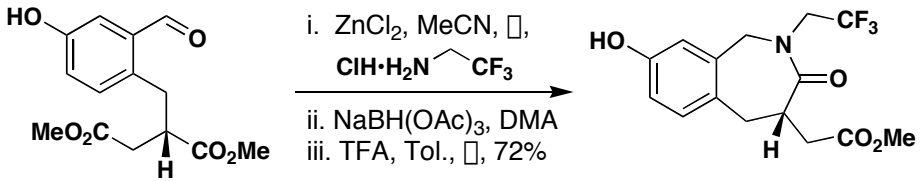
Masterpieces in Process Chemistry

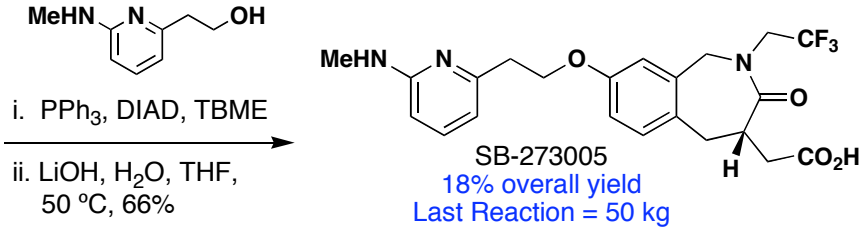
SB-273005



1. Vitronectin receptor antagonist.
2. Synthesis: GlaxoSmithKline, *OPRD*. **2004**, *8*, 738.







SB-273005
18% overall yield
Last Reaction = 50 kg