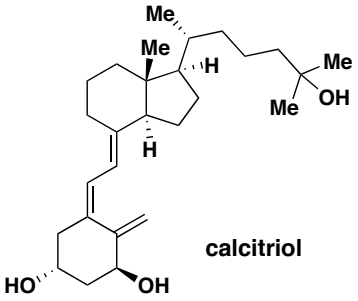
Richter

Masterpieces in Process Chemistry II

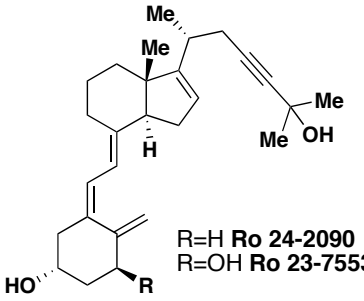
1/11/06
Group Meeting

Selected Syntheses:

Vitamin D Analogs: **Hoffmann-La Roche**

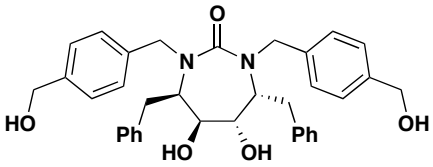


calcitriol

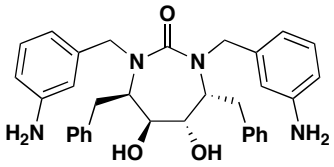


R=H **Ro 24-2090**
R=OH **Ro 23-7553**

HIV Protease Inhibitors: **DuPont-Merck**

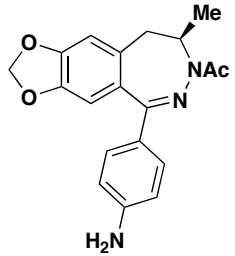


DMP 323



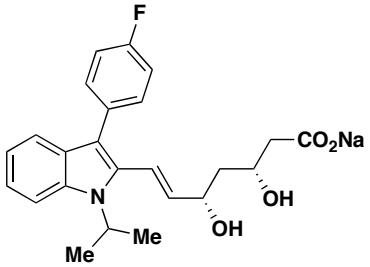
DMP 450

Epilepsy Therapy: **Eli Lilly**



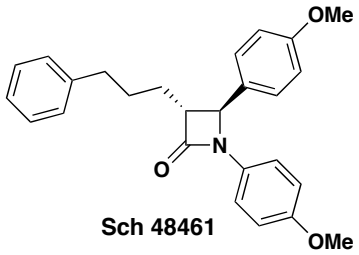
LY300164

Cholesterol Lowering: **Sandoz**

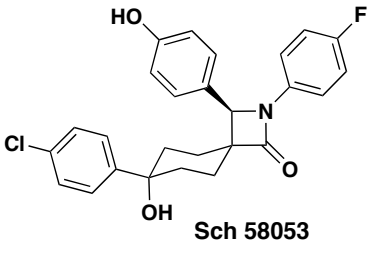


Lescol

Cholesterol Lowering Azetidinones: **Schering Plough**



Sch 48461



Sch 58053

Informative Books on Process Chemistry:

– Gadamasetti, Kumar G. *Process Chemistry in the Pharmaceutical Industry*. Marcel Dekker, Inc. New York: 1999.
– Anderson, Neal G. *Practical Process Research & Development*. Academic Press. San Diego: 2000.
– Repic, Oljan. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry*. John Wiley & Sons, Inc. New York: 1998.

"The mission of process chemistry in the pharmaceutical industry is to provide documented, controlled synthetic processes for the manufacture of supplies to support the development programs and future commercial requirements for an active pharmaceutical ingredient (API) or the drug. The mission represents a tremendous challenge to the synthetic skills of the process scientists as the requirements for drug supply progress from milligrams to metric ton quantities." **– Kumar Gadamasetti**

"The ideal chemical process is that which a one-armed operator can perform by pouring the reactants into a bath tub and collecting pure product from the drain hole." **– Sir John Cornforth**

"Graduate school research in organic synthesis resembles chemical development much more than it resembles medicinal chemistry: Given a target molecule, one must design the synthesis and discover and *develop* all reaction conditions to obtain a reasonable yield of the target molecule." **– Oljan Repic**

"Thus, early on in a project, 'Make stuff!' wins out over 'Learn to make it better!'" **– Richard Mueller**

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Masterpieces in Process Chemistry II

1/11/06
Group Meeting

Practical Considerations for Process Research:

Solvents and Drying:
– Avoid using solid dessicants, azeotrope instead.
– "In general, small, unlike molecules form azeotropes."
– Concentration to dryness is rarely performed, normally solvents are chased out azeotropically.
– Consider using excess reagent to dry the solvents.
– Decanting and siphoning are difficult to perform on scale.
– Solvents avoided: pentane, Et_2O, HMPA (use NMP instead), hexane, PhH, $CHCl_3$, CCl_4, DCM, DCE, ethylene glycol, DME, dioxane, NH_3.
– In general, avoid solvents with flash points below 15 ºC.
– Commonly used solvents: MTBE, heptane, H_2O, MeOH, EtOH, AcOH, *n*-BuOH, *i*-PrOH, MeCN, DMSO, DMF, Acetone, MIBK (good for extractive workups and azeotroping), EtOAc (*i*-PrOAc is better), THF (2-MeTHF allows extractions), PhCl, Tol., TEA, Cyclohexane.
– Stirrability (viscosity) needs to be considered.
– Don't be afraid of multiple solvent systems.
– It is best to use solvents that do not require distillation or purification.
– Optimal concentration is >10%.

Running Reactions:
– To remove oxygen: sparge with N_2 or reflux under N_2.
– Liquids are easier to transfer than solids.
– Acceptable temperature range: –40 to 120 ºC.
– If adding neat liquids to a cooled reaction, the liquid may freeze on the surface, so add as a solution or subsurface.
– Many factors need to be considered when monitoring a reaction: is it a representative sample? Did the sampling and prep time affect the result? Does the temperature increase matter? Determine endpoint based on two samples.
– Reactions requiring anything "rapid" are difficult to perform.
– Be aware of potential exotherms and plan accordingly. May require slower additions, or reflux to absorb the exotherm.
– Consider the following things when choosing reagents: toxicity, side reactivity, expense, availability,consistency between lots, stability, robustness, work-up/quench issues, specialized equipment, solubility.
– Sequence and duration of reagent addition can dramatically affect the outcome.
– To mimic reactions on scale, extend reaction times in the hood.
– Use reagents of low purity before moving to high purity.

Workup:
– Take advantage of natural phase separations.
– Determine the required number and amounts of washes, extractions, etc.
– Be aware of potential quench exotherms.
– Use the smallest number of vessels as possible.
– Add cosolvents (EtOAc, Tol.) or change the pH or electrolyte content to destroy emulsions.
– Consider using activated carbon plugs to remove polar impurities.
– Metals must be removed to cGMP levels.

Cystallizations:
– Each 1% of impurity holds back 1-2% of product.
– Optimize to decrease the nuber of crops required.
– Precipitation is different than crystallization and rarely purifies product.
– Ways to increase crystallization pressure: cool a warmed solution, increase concentration, increase antisolvent, increase ionic strength, control pH.
– Seeding helps crystallization.

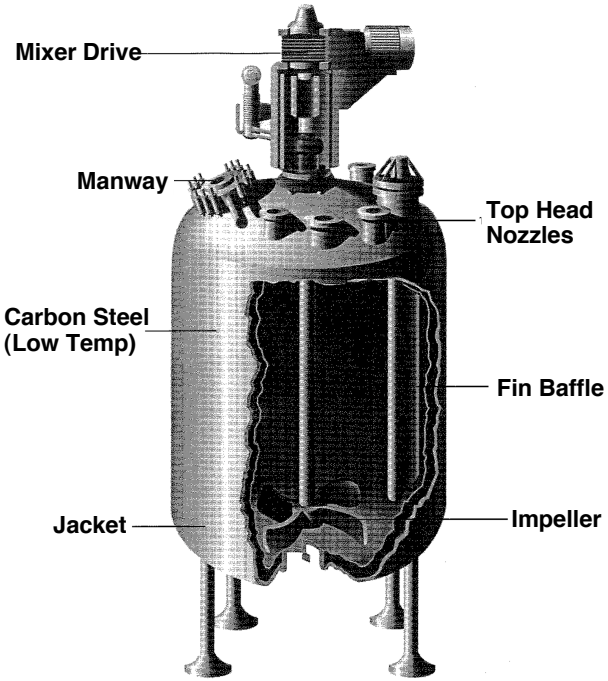
Asymmetric Synthesis on Scale:
– Need greater than 98% *ee*.
– Resolutions (chiral salts, covalent modification, kinetic, enzymatic, recycling, *Preferential Crystallization*).
– Chiral pool (consider that the SM may not be high *ee*)
– Asymmetric induction (metal based, chiral auxiliary, enzymatic): consider recycling, cost, toxicity, synthesis of ligands.
– If a reaction is not enantiospecific or stereospecific, it should be placed at the beginning of a synthetic sequence.

Miscellaneous
– Avoid using protecting groups.
– Avoid excessive oxidation state manipulations.
– Every impurity present in 0.1% or greater amount must be fully characterized and analyzed for toxicity. For this reason it is a good idea to freeze the final steps and purity profile of a process early.
– Each operation on scale generally requires twice as long as in the hood.
– Ideally the API should be producted at lower than $1000/kg.
– As a process chemist, it may be necessary to "make a reaction work instead of "trying something else."

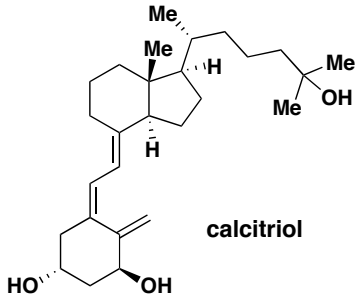
Anderson, Neal G. *Practical Process Research & Development.*

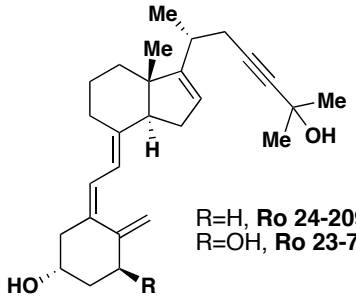
Masterpieces in Process Chemistry II

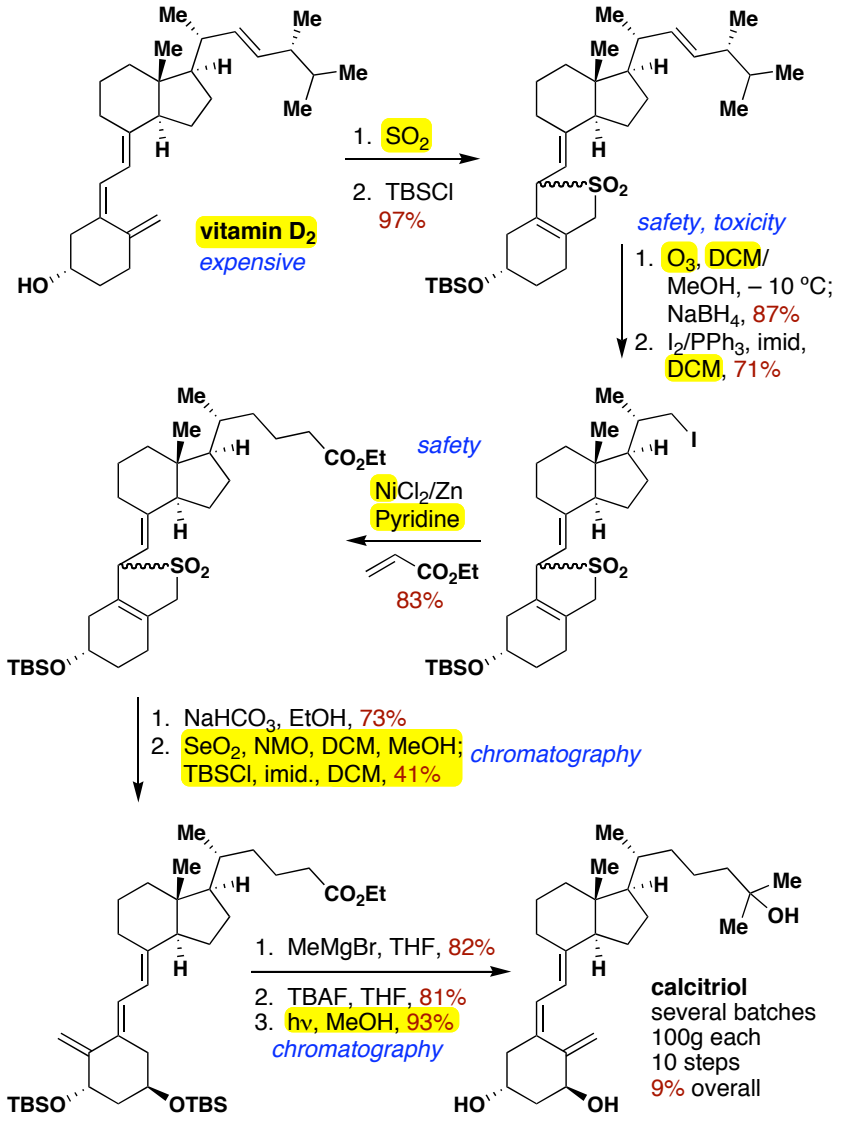
Common Process Reactor:



Vitamin D Analogs:







Gadamasetti, *Process Chemistry in the Pharmaceutical Industry*. Pages 73 – 89.

JOC, **1995**, *60*, 6574.

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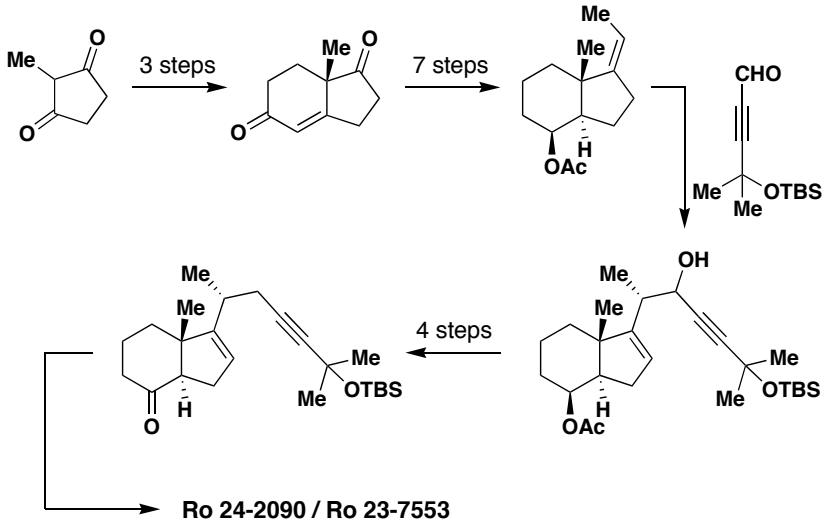
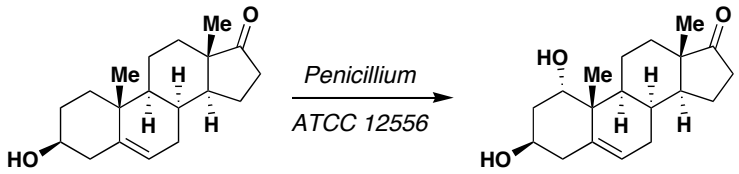
Masterpieces in Process Chemistry II

1/11/06
Group Meeting

Original Med. Chem. route to Ro 24-2090 and Ro 23-7553.

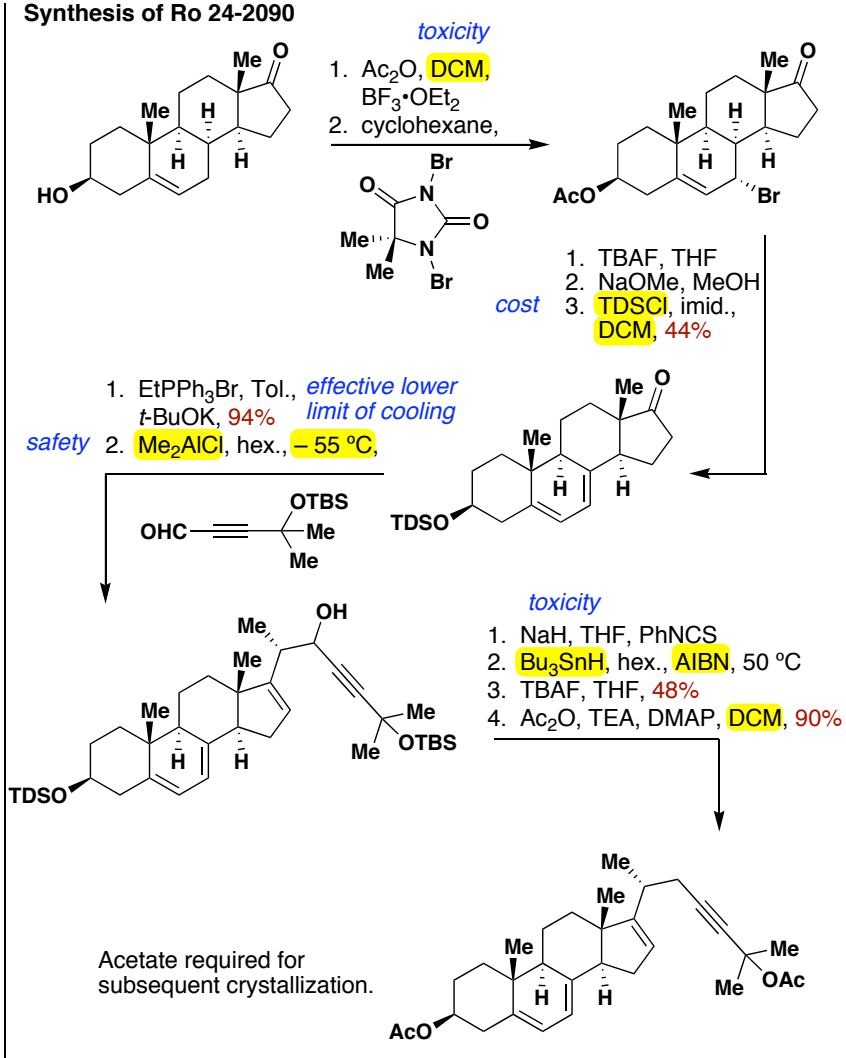


Preparation of starting material for Ro 23-7553.



Note: Fortunately the activity of these compounds is so great that only several hundred grams are required at peak production, allowing more flexibility in scale-up operations, specifically in regards to purification and difficult reaction sequences.

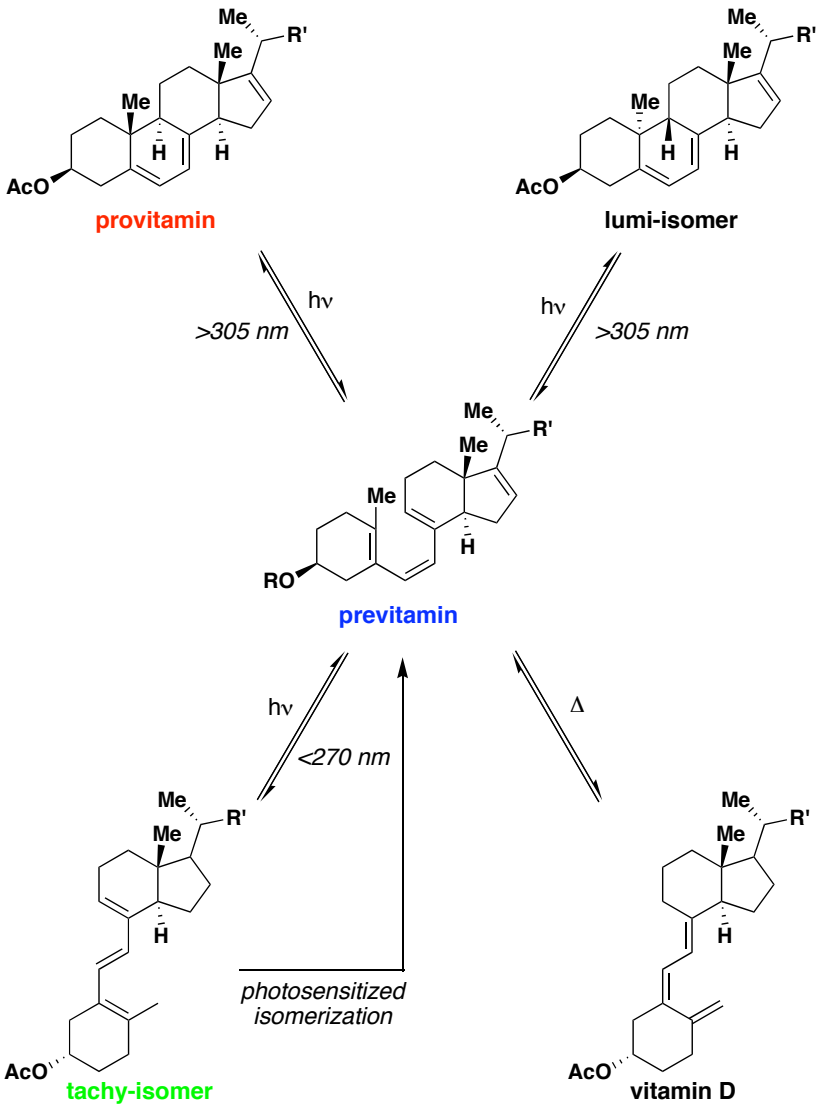
Synthesis of Ro 24-2090



Gadamasetti, *Process Chemistry in the Pharmaceutical Industry.* Pages 73 – 89., *JACS* **1960**, *82*, 4026.

JOC **1995**, *60*, 767.

Masterpieces in Process Chemistry II



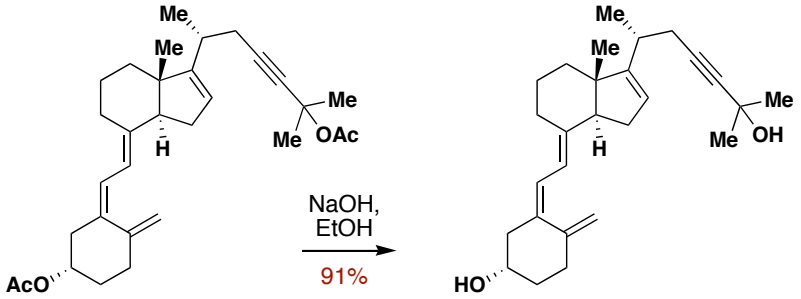
Caveats of running the Reaction:

1. If using mercury lamp with quartz immersion well and optically inactive solvent, tachy is the major product, with less than 15% vitamin D form after thermal isomerization.
2. If using benzene instead, the yield jumps to 15-40%, because the benzene filters out the shorter wavelengths.
3. Use of 305-320 nm light promotes closure to form the pro- and lumi-isomers.
4. Use of 250 nm light then 350 nm light can preferentially form the previtamin, however the specialized equipment is not readily available for scale-up.

Optimized Reaction Conditions:

1. Used a standard 450 W low pressure mercury vapor lamp
2. Irradiate in TBME with ethyl-4-dimethylaminobenzoate for 8 hrs (1:3:2:0)
3. Insert a Uranium filter with 9-acetylanthracene (1:5:<0.1:0)
4. Flash Chromatography
5. Reflux in EtOAc 4 hours to give product below in 39% yield.

NOTE: In previous Med. Chem. syntheses this step proceeded in 15-30% on milligram scale with very difficult HPLC separation to give an oil. This process route produced the first crystals.



Ro 24-2090
Must be stored in solution for stability
13 steps
6% overall
1 Chromatography

Synthesis of **Ro 23-7553** proceeded in an analogous manner albiet with lower yields.

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Masterpieces in Process Chemistry II

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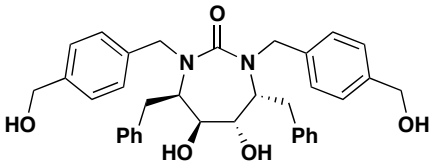
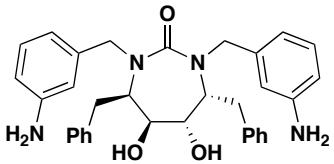
HIV Protease Inhibitors:

– Very interesting story about how structure based drug design has led to a very potent molecule to inhibit the HIV protease. (Patrick Lam, *et.al. J. Med. Chem.* **1996**, *39*, 3514.

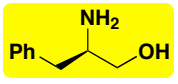


DMP 323



DMP 450

Med. Chem. Route:



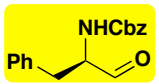
cost (unnatural)

safety

1. CbzCl, 95%
2. Swern, 84%

–78 °C, stench

epimerize & polymerize

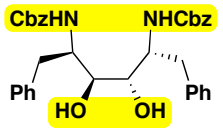


waste stream

Zn/Cu, VCl_3

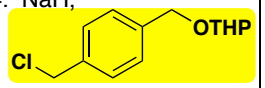
55%

contains carcinogenic impurity



need crystallinaty - protecting groups

1. MEMCl, 81%
2. H_2, Pd/C
3. CDI, DCM, 76%
4. NaH,

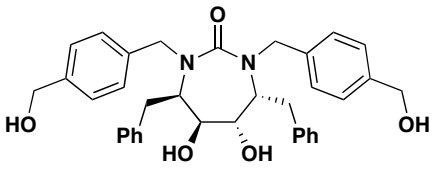


unstable, allowed monoalkylation

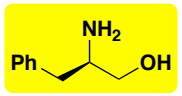
5. HCl, 80%

chromatography

DMP 323
8 steps
23% Overall
final de of 99.5+%
Used for 5 kg in the kilo lab



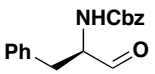
Initial Process Route to DMP 323:



cost (unnatural)

safety

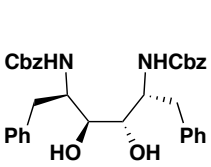
1. CbzCl, 95%
2. NaOCl, NaBr TEMPO, 90%



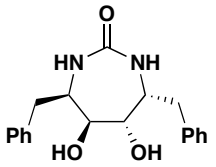
waste stream

Zn/Cu, VCl_3

50%



1. TESCl, imid.
2. H_2, Pd/C
3. CDI
4. HCl, MeCN, H_2O, 78%

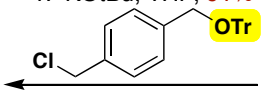


Avoid protecting group switch

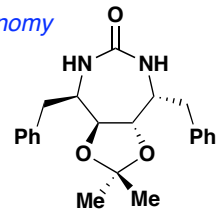
$C(CH_3)_2(OMe)_2$, pTsOH, DMF
95%

atom economy

1. KOtBu, THF, 91%

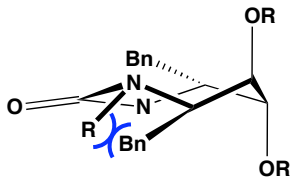


2. HCl, MeOH, Tol., H_2O, 92%

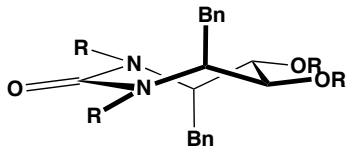


DMP 323
8 steps
27% overall
No chromatography required

Rational for necessity of acetonide to favor bis-alkylation:



vs



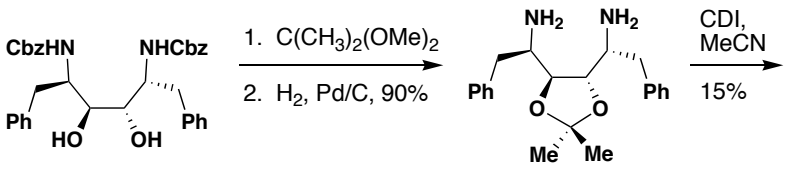
Gadamasetti, Kumar G. *Process Chemistry in the Pharmaceutical Industry*. Pages 201-219.

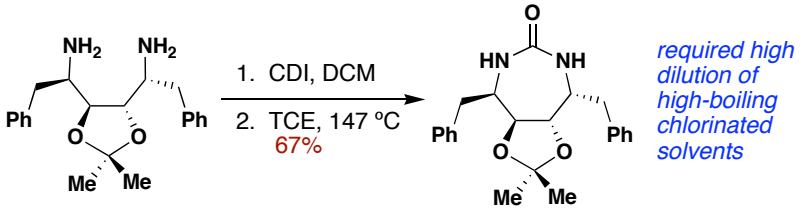
JOC **1996**, *61*, 444.

Masterpieces in Process Chemistry II

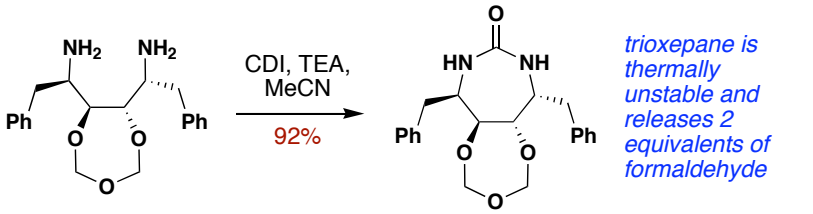
HIV Protease Inhibitors (Continued):

Studies to solve the cyclization problem:





required high dilution of high-boiling chlorinated solvents

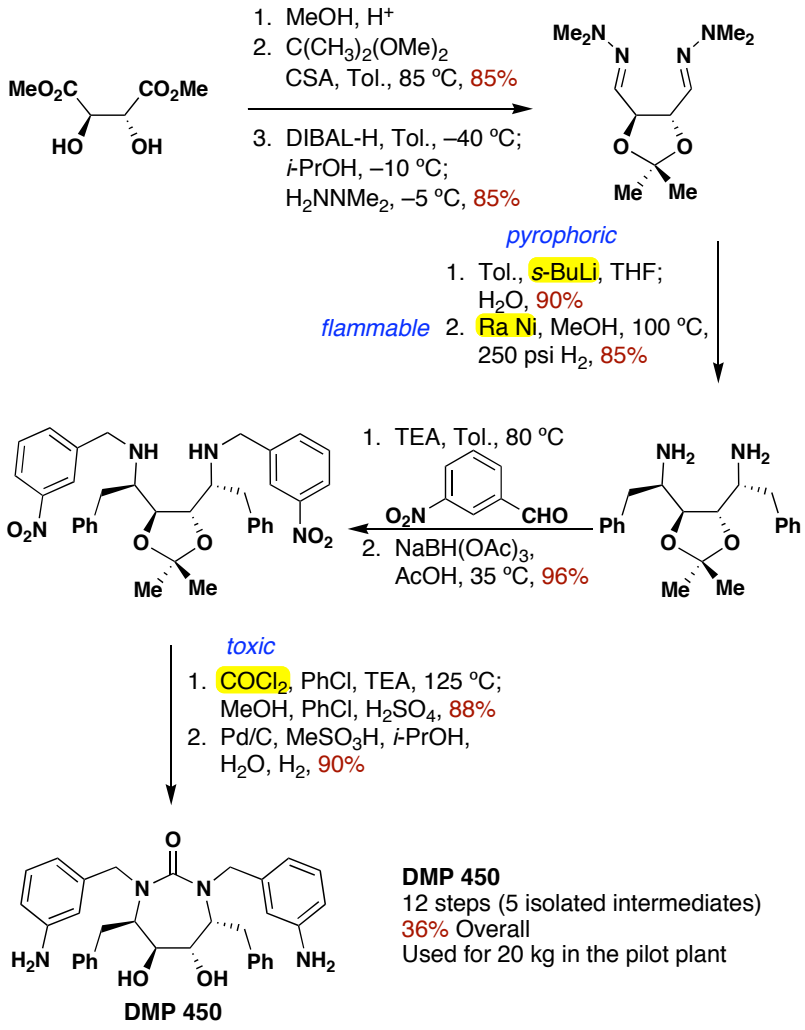


trioxepane is thermally unstable and releases 2 equivalents of formaldehyde

Concurrently, studies were in progess for a more efficient synthesis of the pinacol product.

At this time, **DMP 323** was canceled and **DMP 450** was chosen for development, necessitating an expedient preparation of this compound.

Process Route to DMP 450:



DMP 450

DMP 450
12 steps (5 isolated intermediates)
36% Overall
Used for 20 kg in the pilot plant

Gadamasetti, Kumar G. *Process Chemistry in the Pharmaceutical Industry*. Pages 201-219.

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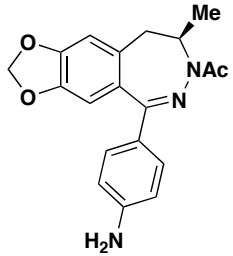
Masterpieces in Process Chemistry II

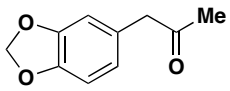
1/11/06
Group Meeting

Epilepsy Therapy:

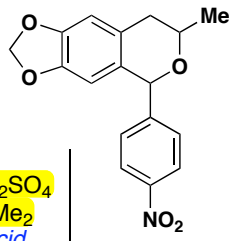


LY300164

Slightly Modified Med. Chem. Route:

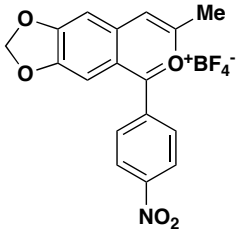


1. $NaBH_4$
2. *p*-NO_2PhCHO, HCl



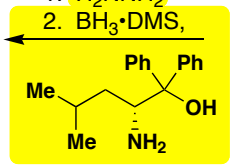
47% yield, Cr waste

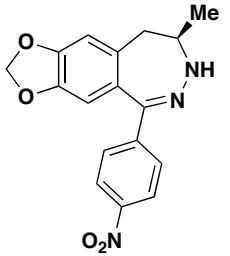
1. CrO_3, H_2SO_4
2. HBF_4OMe_2
strong acid



rocket fuel

1. H_2NNH_2
2. BH_3•DMS,





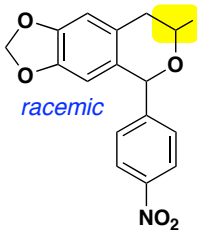
56% yield
stoichiometric auxiliary (expensive)

1. Ac_2O
2. H_2, Pd/C

LY300164
8 steps
14% overall
73% *ee* (raised to 96% w/ recrystallization)

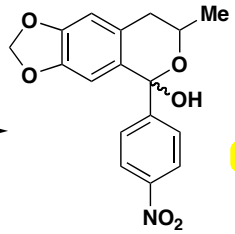
"The most significant issues [with this synthesis] were symptoms of an overall strategic problem which centered on excessive manipulation of oxidation state"

Initial Process Route to LY300164:



racemic

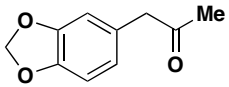
waste
$KMnO_4$,
0 ºC, 70%



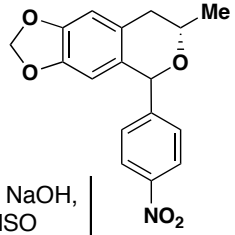
1. H_2NNHAc
2. DIAD, PPh_3
purification

P

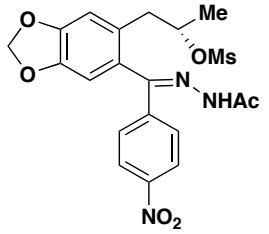
Process Route to LY300164:



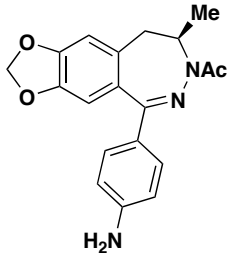
1. *Z. rouxii*, XAD-7
2. *p*-NO_2PhCHO, HCl, 87%



1. air, NaOH, DMSO
2. H_2NNHAc
3. MsCl, TEA, 75%



1. NaOH, EtOH
2. KO_2CH, Pd/C
91%



LY300164
7 steps
3 isolated intermediates
55% overall
99.9% *ee*

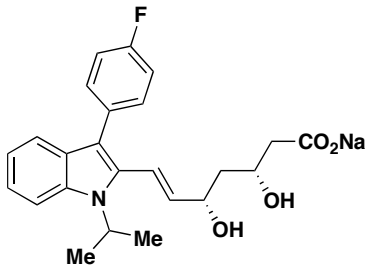
Gadamasetti, Kumar G. *Process Chemistry in the Pharmaceutical Industry*. Pages 263–282.

Richter

Masterpieces in Process Chemistry II

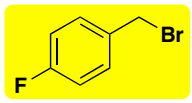
1/11/06
Group Meeting

Cholesterol Lowering Drug:



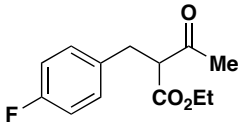
Lescol

Med. Chem. Route:



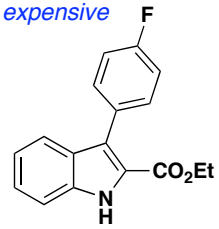
expensive

EtOAcAc



dangerous

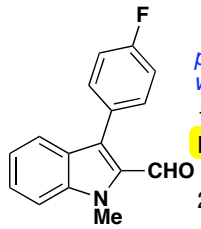
PhN_2^+



toxicity

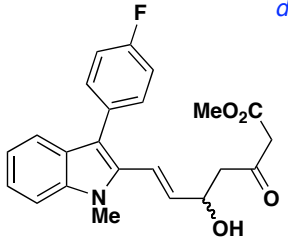
1. NaH, DMA, MeI
2. DIBAL-H
3. MnO_2, Et_2O

dangerous



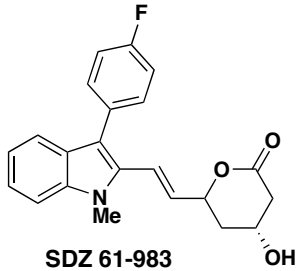
pyrophoric, waste, expensive

1. BuLi, $Bu_3SnCH{=}CHOEt$
2. MeOAcAc



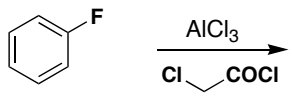
poor de

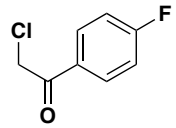
1. *t*-$BuNH_2{\cdot}BH_3$
2. NaOH
3. H^+
4. heat



SDZ 61-983
11 steps
Very low yeilding

First Process Route:

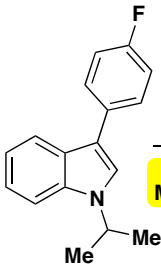




PhNHiPr, EtOH;

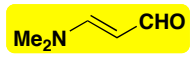
$ZnCl_2$, EtOH, 99%

"Since a 2-formylation of indoles had previously not been reported, we had to invent it."

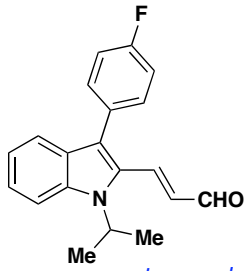


New Reaction

$POCl_3$



cost - 67% of total for route



1. NaH, BuLi, THF, MeOAcAc
2. Et_3B, $NaBH_4$

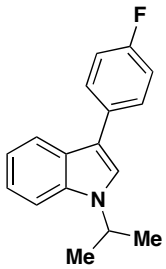
–90 ºC

3. NaOH, H_2O, MeOH

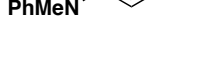
spontaneously flammable
toxic, removing B to 10 ppm
too low temperature
poor selectivity (8:2)

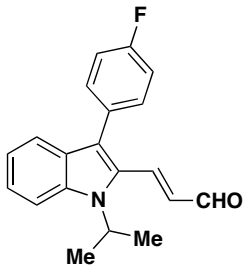
Lescol

freeze drying



$POCl_3$, MeCN, 75%





1. *t*-BuOAcAc, THF
   BuLi, hex., NaH
2. $NaBH_4$, THF
   Et_2BOMe, MeOH;
   H_2O_2, 73%
3. NaOH, EtOH, H_2O

Lescol
6 steps
54% overall

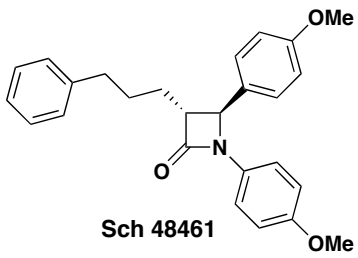
Repic, Oljan. *Principles of Process Research and Chemical Development in the Pharmaceutical Industry.* *JOC*, **1992**, *57*, 3250.

Richter

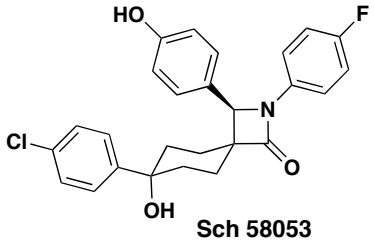
Masterpieces in Process Chemistry II

1/11/06
Group Meeting

Cholesterol Lowering Drug:

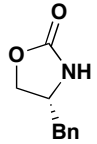


Sch 48461

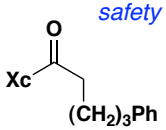


Sch 58053

Process Route to Sch 48461:

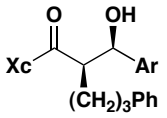


BuLi, THF;
$Ph(CH_2)_4COCl$

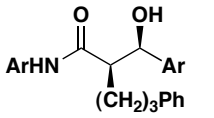


pyrophoric, expensive, safety issues

Bu_2BOTf, DIPEA, –78 °C;
p-anisaldehyde
85%



1. LiOH, H_2O_2
2. *p*-anisidine, HOBT, DCC
80%

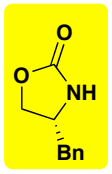


toxic

Bu_3P, DEAD,
80%

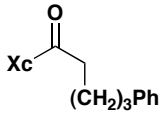
required 2 chromatographies (on one step)

Sch 48461
5 steps
54% overall
>99.9% *ee*

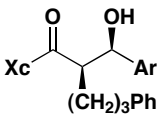


expensive (unnatural)

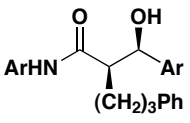
TEA, DMAP;
$Ph(CH_2)_4COCl$



$TiCl_4$, TEA, TMEDA, –20 °C;
p-anisaldehyde
78%



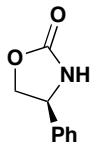
1. LiOH, H_2O_2 THF, H_2O
2. *p*-anisidine, HOBT, DCC DCM, 80%



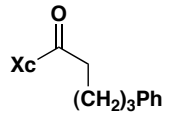
$(EtO)_2POCl$, 50% NaOH
PTC, 85%

still required 1 chromatography

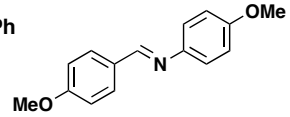
Sch 48461
5 steps
53% overall

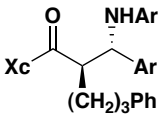


TEA, DMAP;
$Ph(CH_2)_4COCl$



$TiCl_4$, DIPEA, –20 °C; 65%,

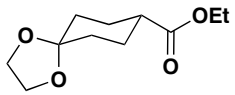




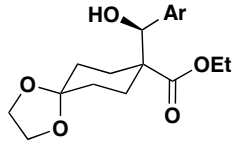
BSA; TBAF (cat.); MeOH
85%

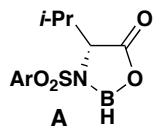
Sch 48461
3 steps
55% overall

Process Route to Sch 58053:

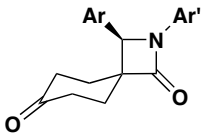


1. LDA, TMSCl, 95%
2. 4-BnOC_6H_4CHO, **A**; TBAF, 90%





1. $4\text{-FC}_6H_4NH_2$, Me_3Al
2. $(EtO)_2POCl$, 50% NaOH, PTC, 59%



1. 4-ClC_6H_4MgBr, 80 °C, 90%
2. 10% Pd/C, $ZnBr_2$, 70%

Sch 58053
6 steps
32% overall

Gadamasettie, Kumar G. *Process Chemistry in the Pharmaceutical Industry.* Pages 221 – 242.