

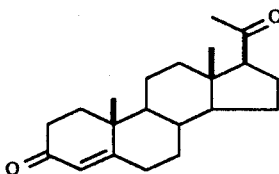
# Recent Advances in Pharmaceutical Process R&D

## Progesterone Tipranavir

IASOC 2000  
Joseph M. Timko, Ph.D.  
Chemical Process R&D

**PHARMACIA**

## Progesterone



- 1934 - Isolation and characterization.
- Progestational agent

### Chemical Intermediate:

Hydrocortisones  
Predni-steroids  
Highly functionalized  
steroids

75%



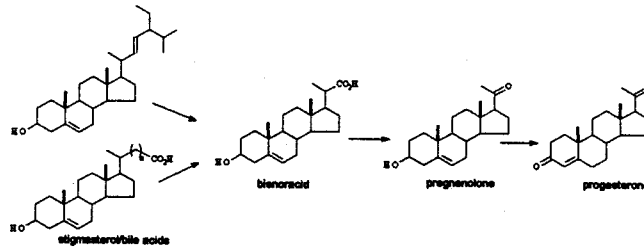
25%

### Drug Products:

Corlutin, Cyclogest,  
Gestone, Luteol, Lutren,  
Progestogel, Proluton,  
Ultrogestan, etc

**PHARMACIA**

## Historic Progesterone Syntheses

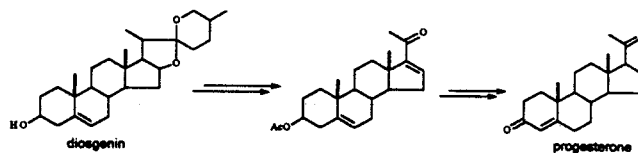


### ISSUES

- /// Lengthy inefficient processes
- /// Hazardous - toxic reagents
- /// Expensive!

**PHARMACIA**

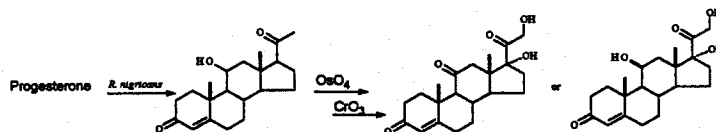
## First Commercially - Attractive Synthesis



- /// Diosgenin-based
- /// Syntex
- /// \$100s/gm → \$1s/gm

**PHARMACIA**

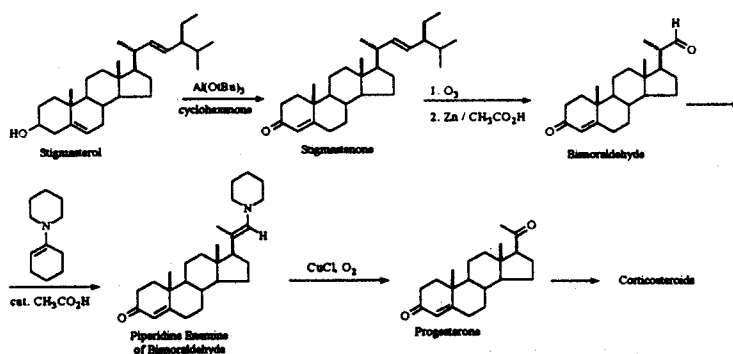
## Progesterone to Corticosteroids



- /// Corticoid demand greater than progesterone
- /// Upjohn based process
- /// \$1s/gm  $\rightarrow$  \$0.10s/gm

**PHARMACIA**

## Heyl-Herr Process



- /// Stigmasterol is minor component of soya sterol feedstock
- /// 8.4 L aqueous waste per kg bismoraldehyde
- /// 3 L of non-recoverable organic waste per kg bismoraldehyde

**PHARMACIA**

### Greiner-Fevig Counter Current Crystallization

Soya Sterols

stigmasterol + sitosterols + campesterol + misc.

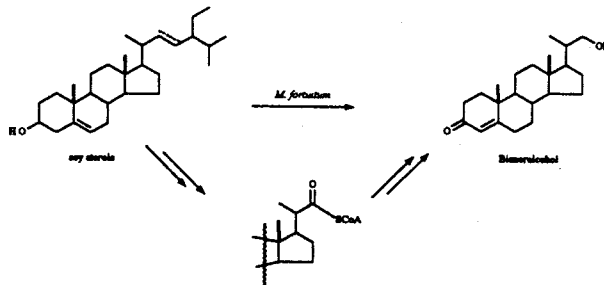
Sterol Residue  
7100 kg

Stigmasterol  
1700 kg, 90% pure

- ⚡ Azeotrope 63% EDC - 37% n-heptane
- ⚡ 230,000 L EDC closed-loop inventory
- ⚡ 19,000 L virgin EDC required annually

**PHARMACIA**

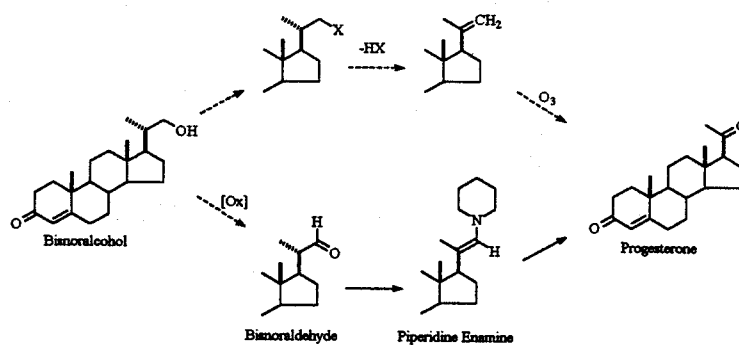
### Bisnoralcohol Bioconversion



- ⚡ Independent of side chain
- ⚡ Bisnoracid derivative as intermediate
- ⚡ Absence of bisnoracid critical downstream

**PHARMACIA**

## Bisnoralcohol Utilization



### Considerations:

- /// Progesterone Regulatory Files
- /// Development resources and time

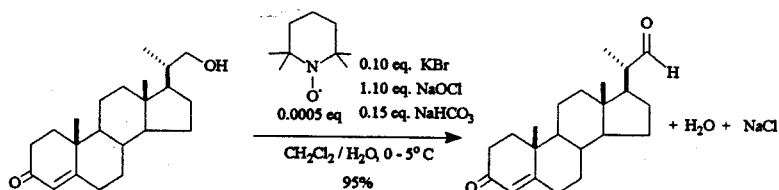
**PHARMACIA**

## Criteria for Bisnoralcohol Oxidation

- /// Safe
- /// Environmentally Friendly
- /// Selective (aldehyde vs acid)
- /// Economical
- /// Reliable

**PHARMACIA**

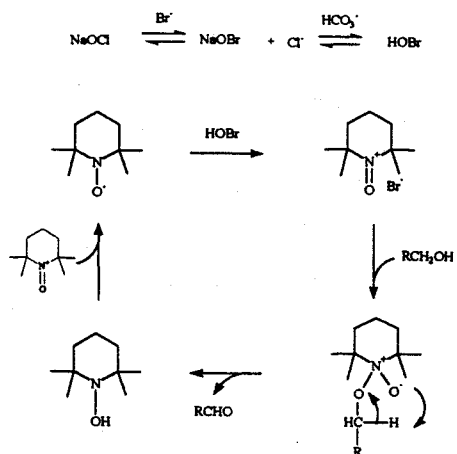
## Nitroxyl Catalyzed Bleach Oxidation



Anelli, P.L., et. al. *J. Org. Chem.* 1987, 52, 2559.

**PHARMACIA**

## Mechanism of TEMPO Oxidation



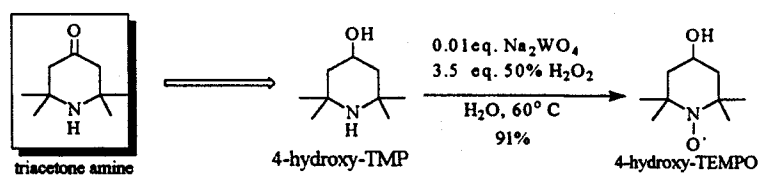
**PHARMACIA**

## Initial Evaluation

- /// Green: Concentrated, biphasic reaction, closed loop solvents, non-toxic waste
- /// Selective: Less than 1% bisnoracid, but catalytic activity and accurate endpoint determination are critical.
- /// Safe: No material or operational hazards, but reaction is fast and exothermic.
- /// Economical: Competitive with low TEMPO loading.

**PHARMACIA**

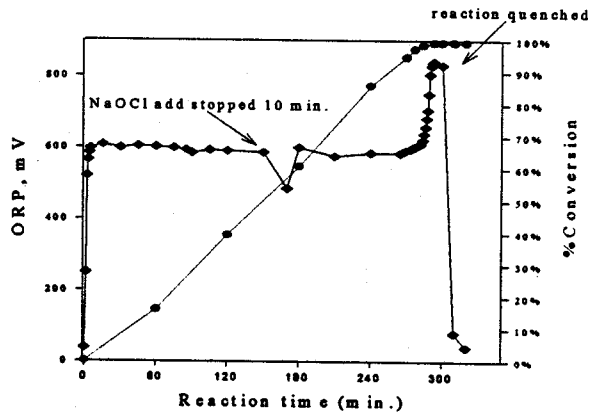
## TEMPO Replacement



**PHARMACIA**

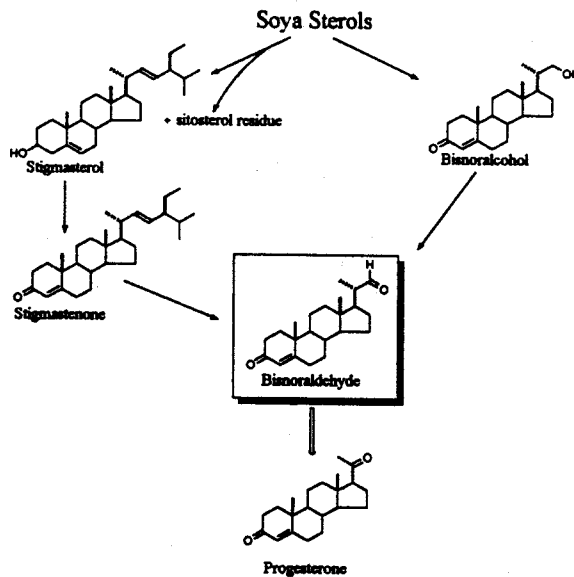
## On-line Endpoint Determination Using ORP Probe

ORP Response and Reaction Progress vs. Time



**PHARMACIA**

## Summary



**PHARMACIA**

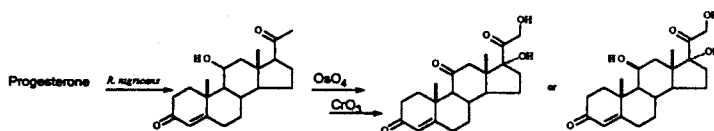


## Achievements

- /// Eliminated the use of EDC and Oppenauer oxidation
- /// Reduced non-recoverable organic waste by 89%
- /// Reduced aqueous waste by 72%
- /// Equivalent quality & reliability of Progesterone process
- /// Avoided use of toxic or hazardous reagents
- /// Increased feedstock utilization from 16% to 100%

**PHARMACIA**

## Work in Progress



- /// Replace Chromium with Bromate
- /// Alternate Pathways which avoid OsO<sub>4</sub> Chemistry

**PHARMACIA**

## Bisnoralcohol Team

### BIOPROCESS

Merle Wovcha  
Kevin Short  
John Ceglarek  
Norm Jansen  
Omar Salman  
David Brunner

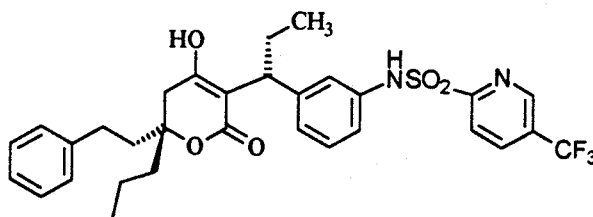
### CHEMISTRY

Bradley Hewitt  
John Wachter  
M. D. Pillai  
Holly Little  
Carol Mitchell  
Donald Knoechel  
John Knight  
Verlan VanRheenen

---

**PHARMACIA**

## TIPRANAVIR



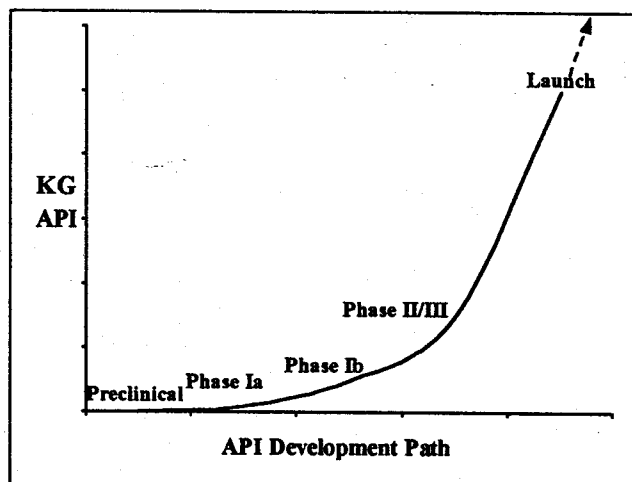
**PNU-140690**

- Non-peptidic HIV Protease Inhibitor (PI).
- Targets PI-Resistant AIDS virus.

---

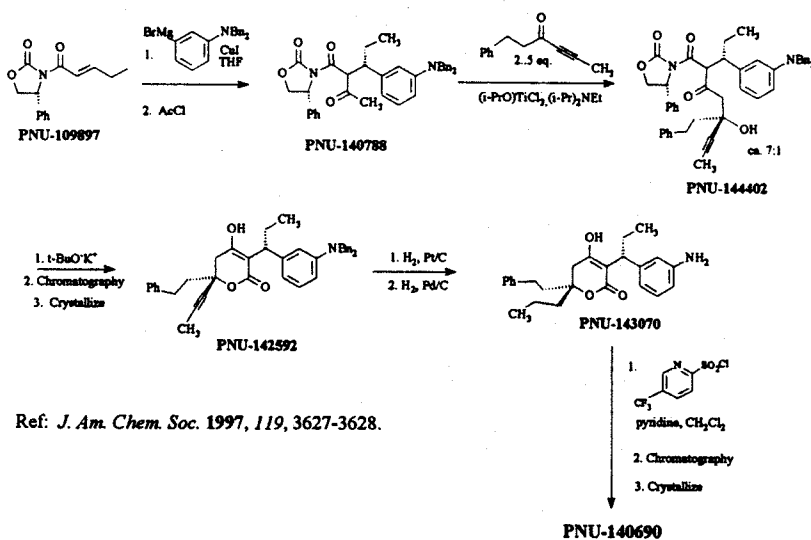
**PHARMACIA**

## The Pipeline: An API Supply Perspective



**PHARMACIA**

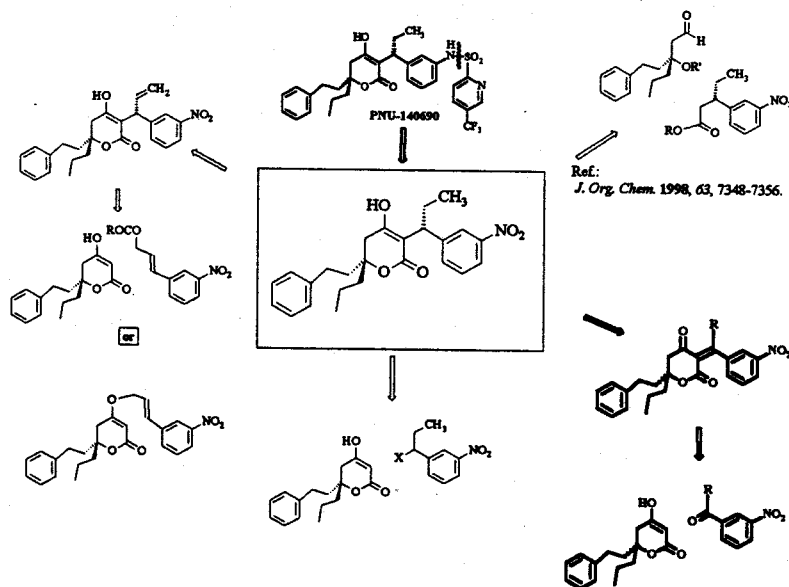
## MedChem Route



Ref: *J. Am. Chem. Soc.* 1997, 119, 3627-3628.

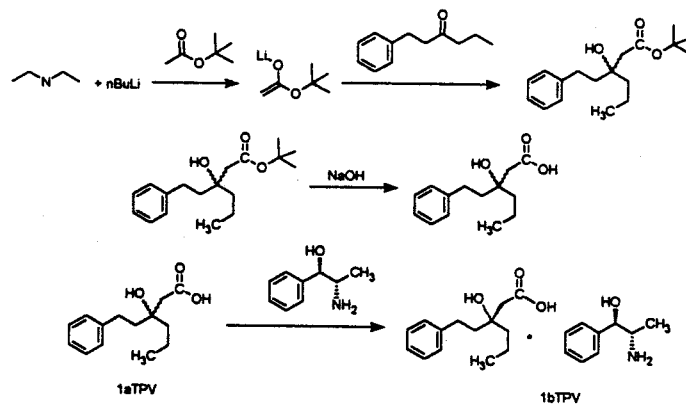
**PHARMACIA**

## Retrosyntheses



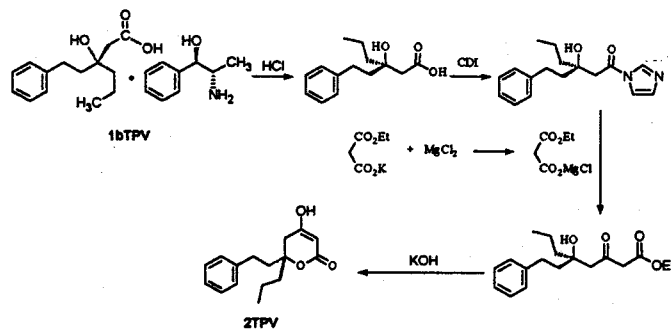
**PHARMACIA**

## Chiral Hydroxy-Acid



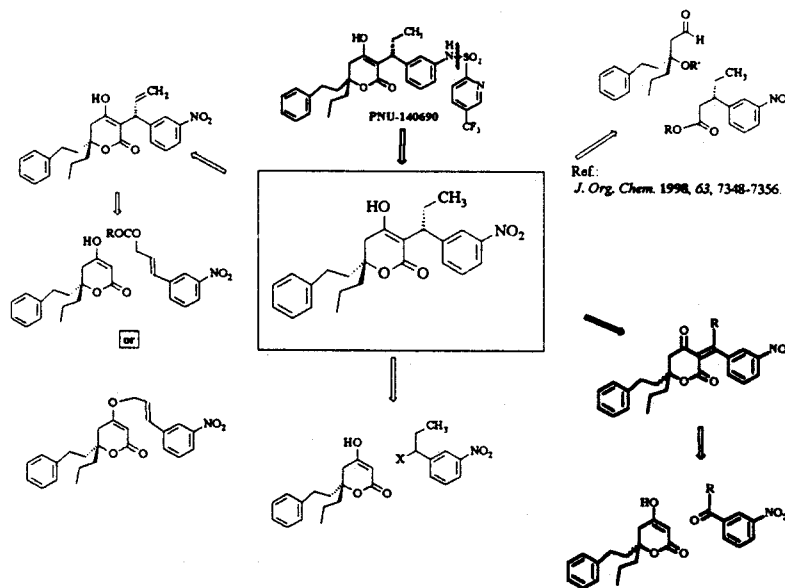
**PHARMACIA**

## Chiral Dihydropyrone



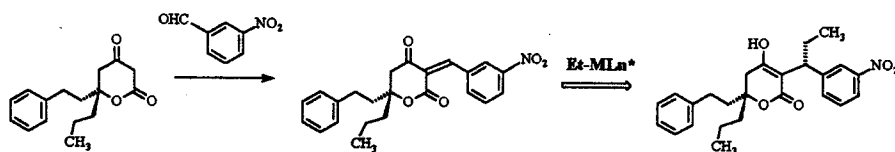
**PHARMACIA**

## Retrosyntheses

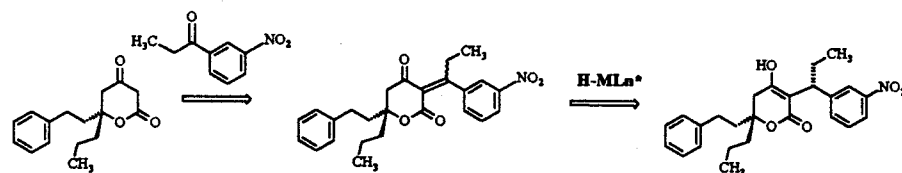


**PHARMACIA**

## Knoevenagel Approaches

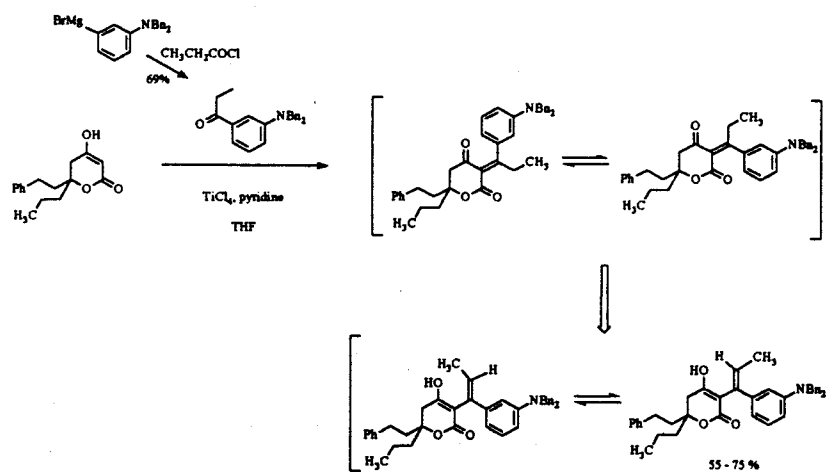


Ref: *J. Med. Chem.*, 1996, 39, 4630-4642



**PHARMACIA**

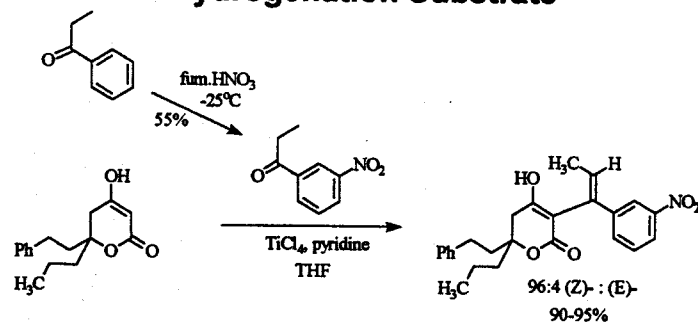
## Initial Success



Ref: Lehnert, W. *Tetrahedron*, 1973, 635-638.

**PHARMACIA**

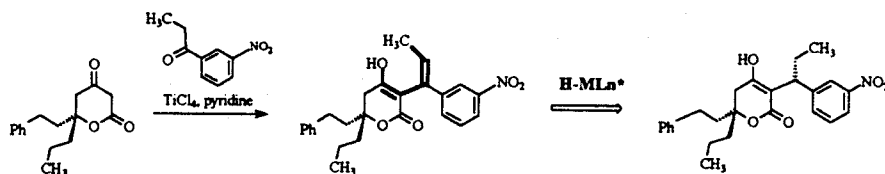
## Hydrogenation Substrate



- Non-Crystalline
- Not Isolated

**PHARMACIA**

## The Big Question



- Empirical approach
- Outside collaboration

### Catalyst Criteria:

- Diastereoselectivity
- Chemoselectivity
- Efficiency
- Cost (meets COG needs)

### Ru-catalysts:

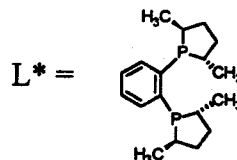
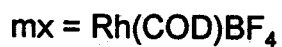
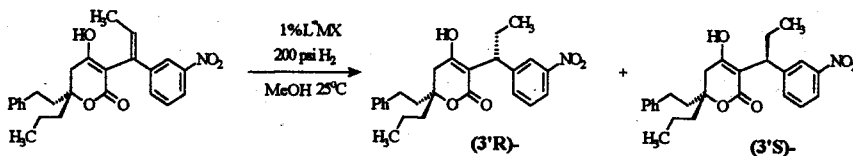
- Low d.e. (38% at best)
- Chemoselective at  $T < 90^\circ\text{C}$ .

### Rh-catalysts:

- High d.e. (93%)
- Potential nitro reduction at  $50^\circ\text{C}$ .

**PHARMACIA**

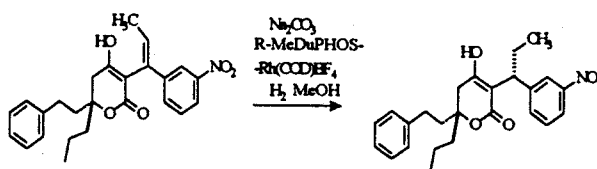
### The Answer



- Solvent
- Pressure
- Temperature
- Base Catalysis
- Catalyst Loading

**PHARMACIA**

### Hydrogenation Implementation & Scale Up



#### “Technical Difficulties”

- Slow, stalled reactions
  - oxygen
- Extensive nitro reduction
  - equipment contamination

#### Success at last:

- GT 99% Conversion
- Average d.e. : 90.2%
- Crystallized: GT 99% d.e.
- 100 kilo scale

**PHARMACIA**



