Recent Advances in Pharmaceutical Process R&D

Progesterone
Tipranavir

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

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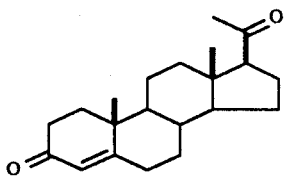
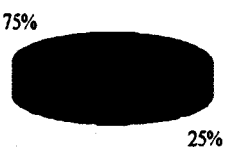
Progesterone



- 1934 -Isolation and characterization.
- Progestational agent

Chemical Intermediate:

Hydrocortisones
Predni-steroids
Highly functionalized steroids



Drug Products:

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

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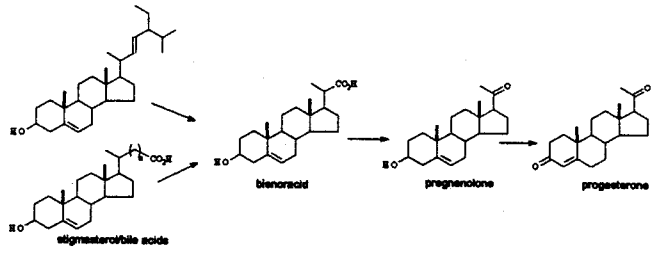
Historic Progesterone Syntheses



ISSUES

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

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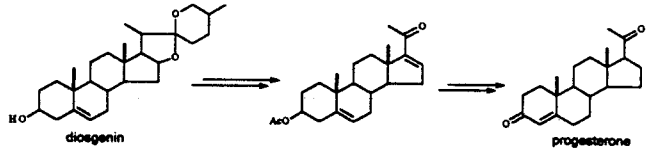
First Commercially - Attractive Synthesis



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

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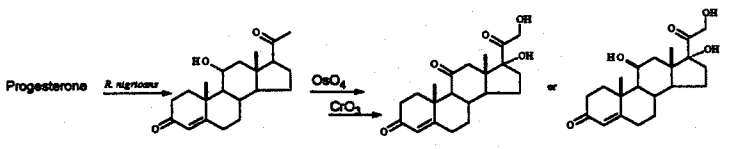
Progesterone to Corticosteroids



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

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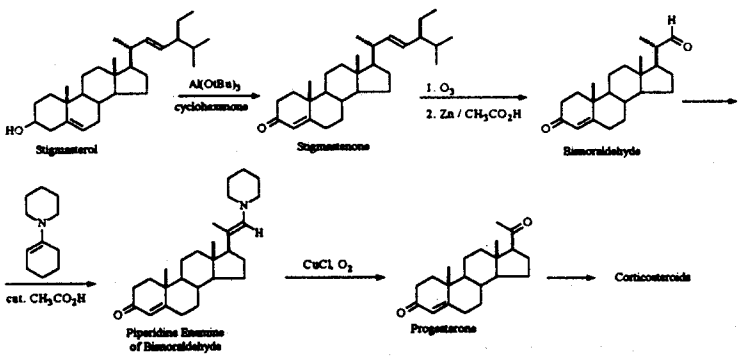
Heyl-Herr Process



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

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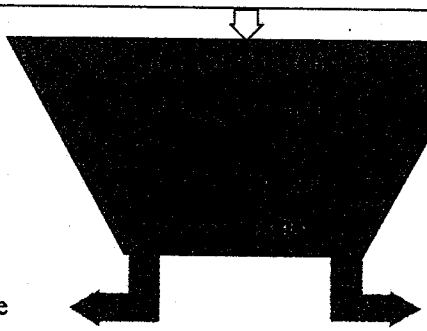
Greiner-Fevig Counter Current Crystallization

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**

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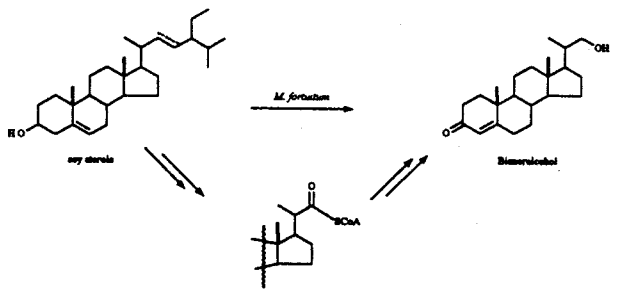
Bisnoralcohol Bioconversion



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

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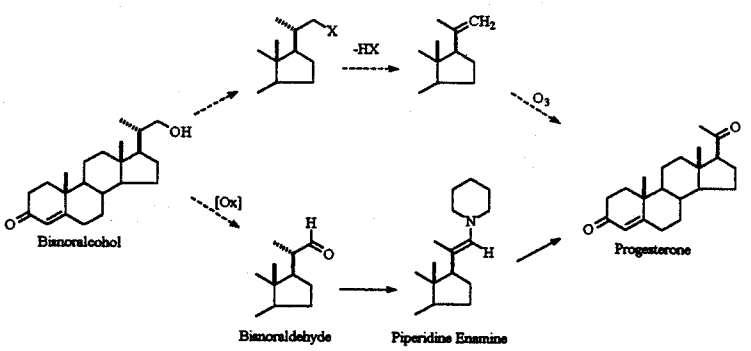
Bisnoralcohol Utilization



Considerations:

- Progesterone Regulatory Files
- Development resources and time

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Criteria for Bisnoralcohol Oxidation

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

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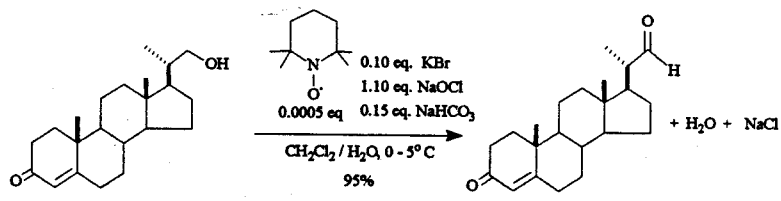
Nitroxyl Catalyzed Bleach Oxidation



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

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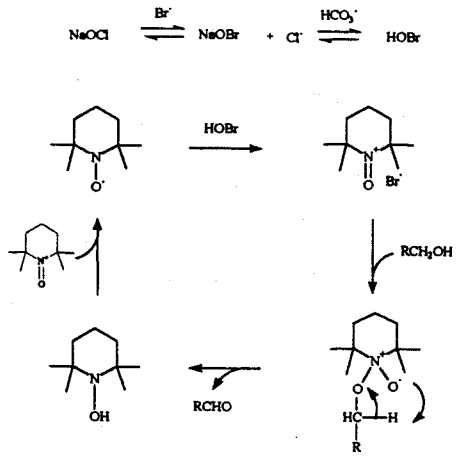
Mechanism of TEMPO Oxidation



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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.

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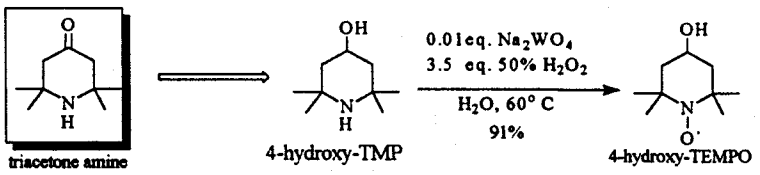
TEMPO Replacement



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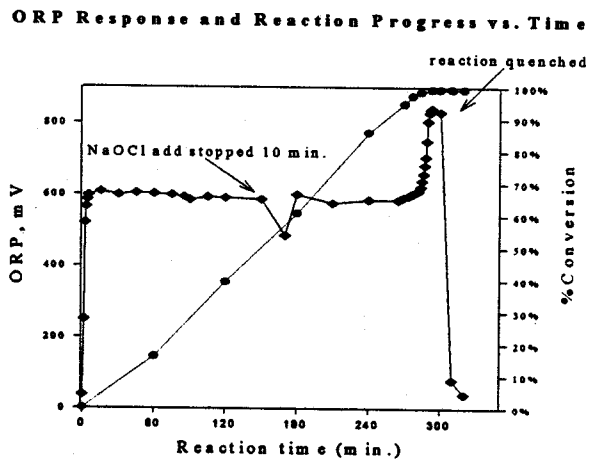
On-line Endpoint Determination Using ORP Probe



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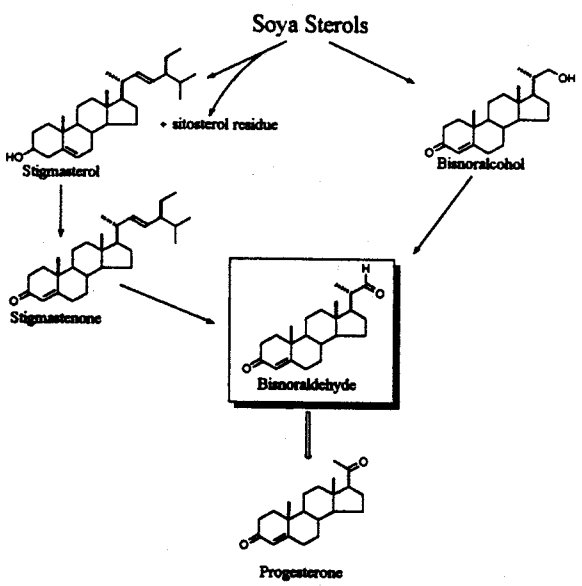
Summary



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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%

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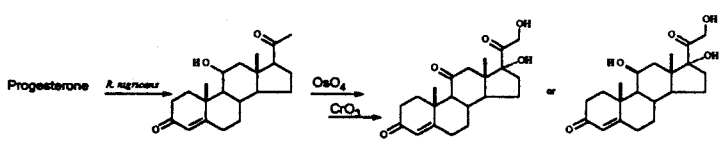
Work in Progress



- Replace Chromium with Bromate
- Alternate Pathways which avoid OsO_4 Chemistry

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Bisnoralcohol Team

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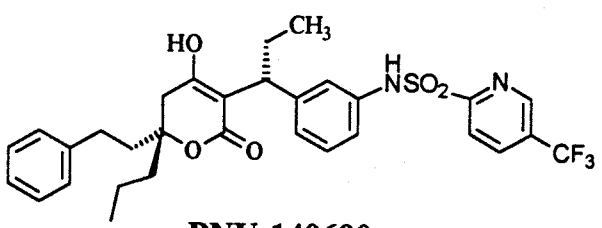
TIPRANAVIR



PNU-140690

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

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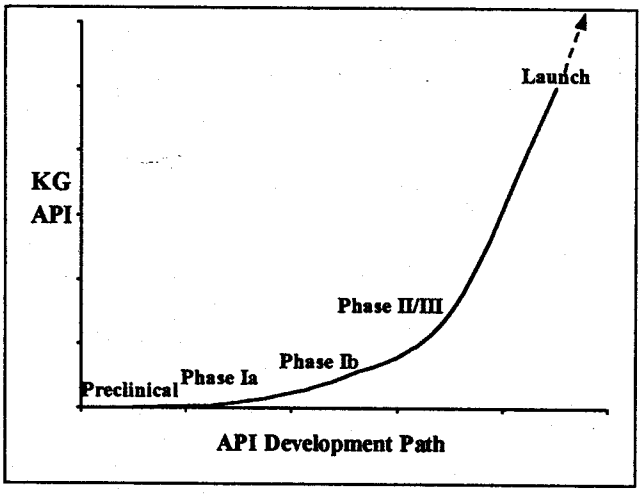
The Pipeline: An API Supply Perspective



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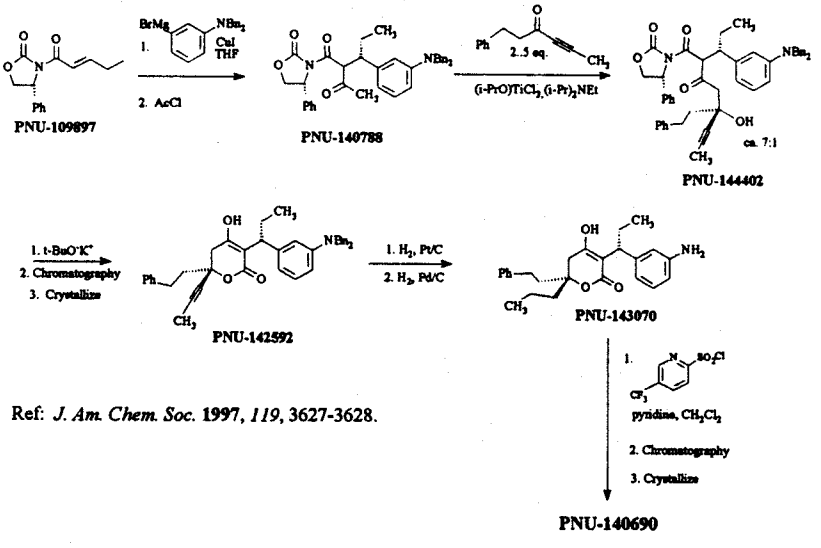
MedChem Route



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

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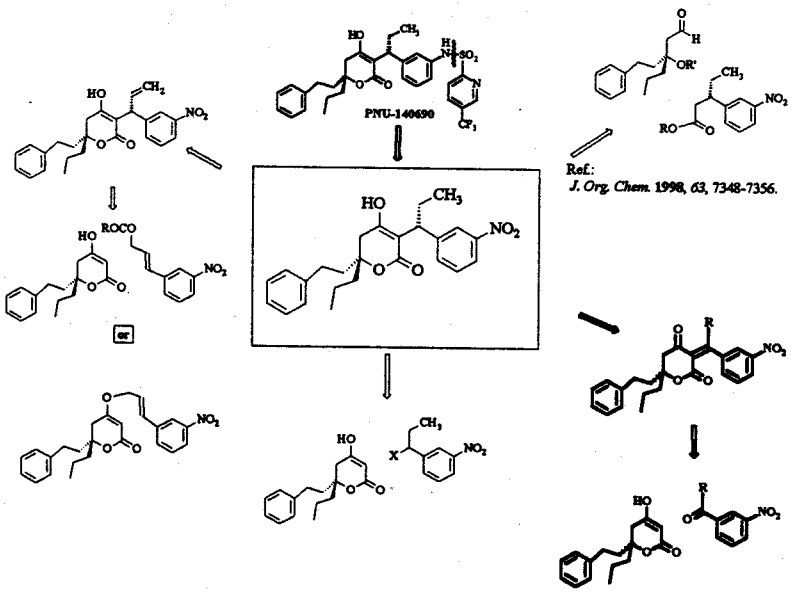
Retrosyntheses



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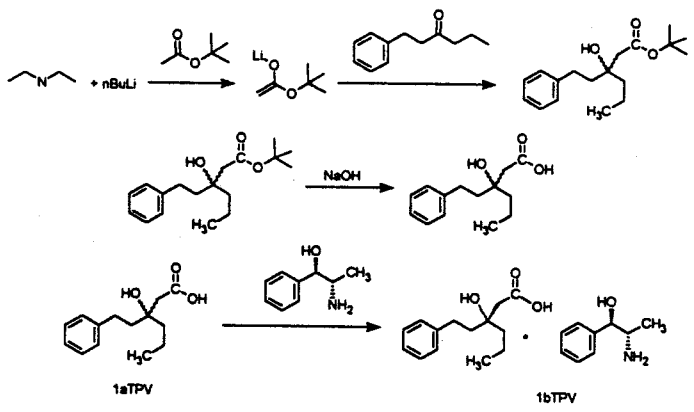
Chiral Hydroxy-Acid



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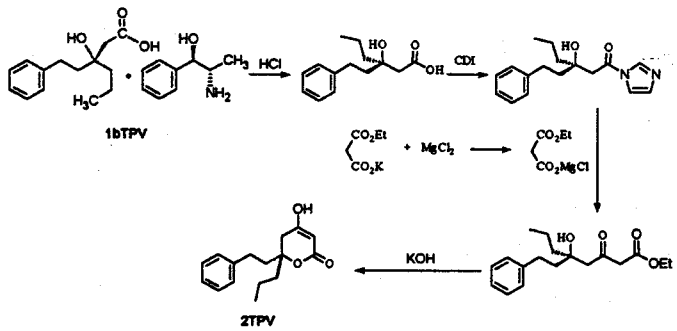
Chiral Dihydropyrone



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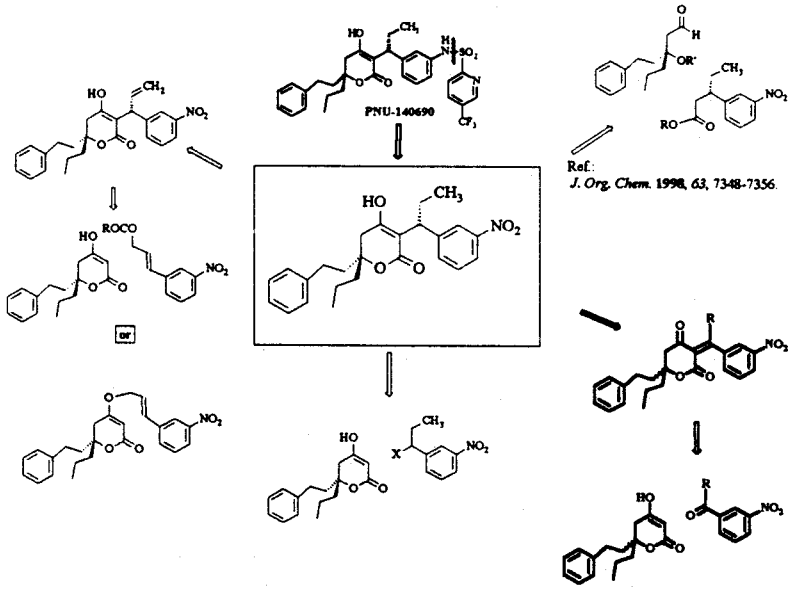
Retrosyntheses



Ref.:
J. Org. Chem. 1998, *63*, 7348-7356.

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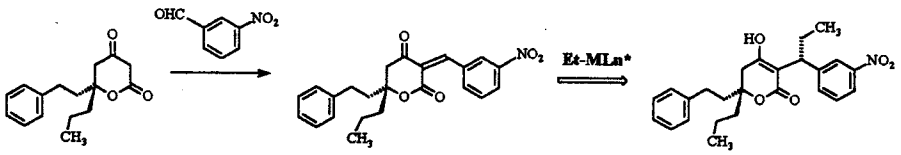
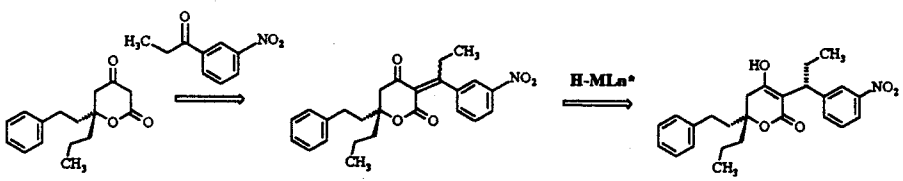
Knoevenagel Approaches



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



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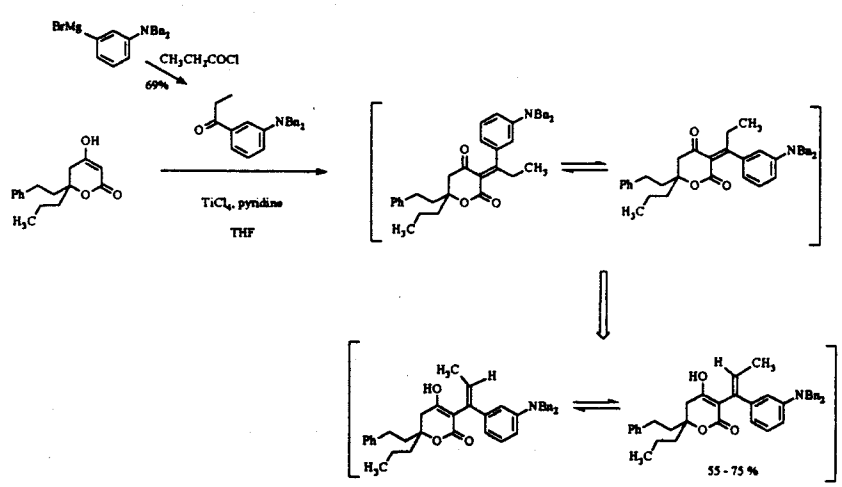
Initial Success



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

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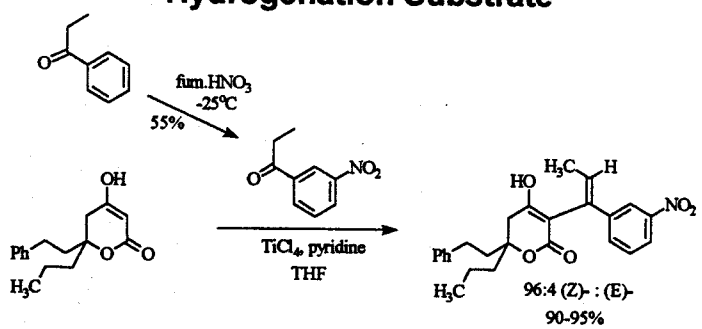
Hydrogenation Substrate



- **Non-Crystalline**
- **Not Isolated**

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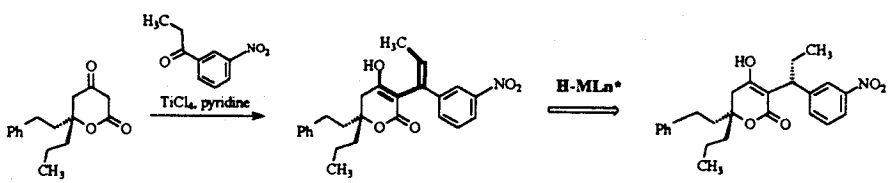
The Big Question



- **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 °C.

Rh-catalysts:

- High d.e.(93%)
- Potential nitro reduction at 50 °C.

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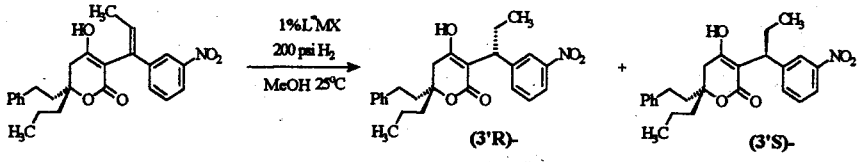
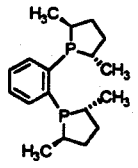
The Answer



mx = $Rh(COD)BF_4$

L* = 

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

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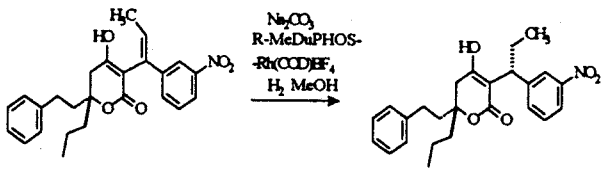
Hydrogenation Implementation & Scale Up



"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

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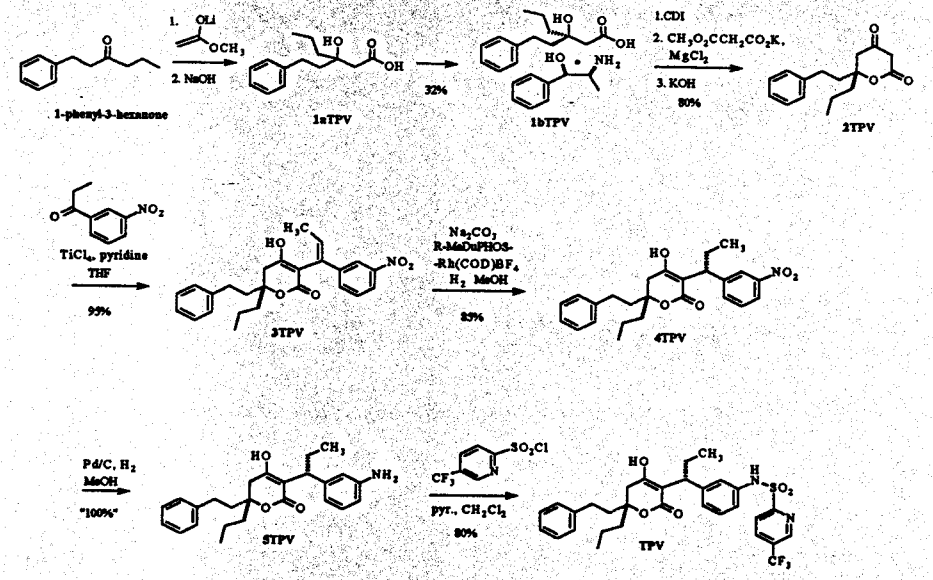
Synthesis Summary



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