Classics in Pharmaceutical Process Chemistry

MAY I TAKE YOUR PICTURE FOR A FEATURE STORY IN "GULLIBLE WORLD" MAGAZINE?

IT'S A STORY ABOUT HOW ENGINEERING MAKES YOU SEXIER.

GOSH, OKAY.

PERFECT. NOW ALL I NEED IS SOMEONE TO POSE FOR THE "AFTER" PICTURE.

Jen Alleva, 11 December 2014

MacMillan Group Meeting
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

- **Discovery**
- **Preclinical Development**
- **Exploratory Development**
- **Development/Life Cycle Management**
- **Launch**

Phase I: early scale-up
Phase IIa
Phase IIb: multi-kilo delivery
Phase III
Phase IV
Evolution of Pharmaceutical Process Research and Development

A Historical Perspective

1688, founding of Merck

"18th Century"

founding of Geigy, Hoescht
Bayer, ICI
Evolution of Pharmaceutical Process Research and Development

A Historical Perspective

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

1880's Bayer and Hoechst launch first pharmaceuticals

Kairin (Hoechst) phenacetin (Bayer)

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

The birth of Process R&D
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

1688, founding of Merck

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

1880's Bayer and Hoechst launch first pharmaceuticals

1914: Eli Lilly implements first written internal regulations: SOP's
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1932: Bayer launches first commercial antibiotic

prontosil
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1950–1953: Merck's synthesis of Cortisone

Desoxycholic acid

Cortisone

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Desoxycholic acid

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1880's Bayer and Hoechst launch first pharmaceuticals

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1950–1953: Merck's synthesis of Cortisone
Classic Syntheses in Pharmaceutical Process Research and Development

Methyldopa

Imipenem

Efavirenz

Darunavir

Prostaglandin E₁
The Merck Synthesis of L-Methyldopa

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

1. nitroethane, K₂CO₃, MeNH₂•HCl
2. Cu, HCl aq., FeCl₃

HCl hydrolysis

resolution of acetamidonitrile

Grabowski, E. J. J. *Chirality*, 2005, 17, S249
The Merck Synthesis of L-Methyldopa

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

1. nitroethane, $\text{K}_2\text{CO}_3$, MeNH$_2$•HCl
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HCl hydrolysis

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The Merck Synthesis of L-Methyldopa

Continuous Flow Resolution Provides both Enantiomers of Methyldopa

resolution of acetamidonitrile

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

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

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Paul Reider
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 $\rightarrow$ 6 steps $\rightarrow$ methyldopa

practical synthesis still in use today for the manufacture of Methyldopa

Merck's asymmetric alkylation via PTC:

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

Grabowski, E. J. J. Chirality, 2005, 17, S249
Classic Syntheses in Pharmaceutical Process Research and Development

Methyldopa

Imipenem

Efavirenz

Darunavir

Prostaglandin E₁
The Merck Synthesis of Imipenem

*The First Carbapenem Antibiotic*

- Thienamycin
- Imipenem

- 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

The Merck Synthesis of Imipenem

Merck's First Generation Process Synthesis

1. CIP-(O)(OPh)₂, DMAP
   Hunig's base, MeCN, 0 °C
   quantitative

2. Hunig's base, MeCN, –5 °C

H₂, 40psi, Pd/C (10 mol%) → thienamycin

19 chemical steps

The Merck Synthesis of Imipenem

Merck's Second Generation Process Synthesis: Current Manufacturing Route

The Merck Synthesis of Imipenem

Merck’s Second Generation Process Synthesis: Current Manufacturing Route

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

Grabowski, E. J. J. *ACS Symposium Series, 2004*, 870 (Chemical Process Research)
The Merck Synthesis of Imipenem

*The First Carbapenem Antibiotic*

\[
\text{Thienamycin} \quad \longrightarrow \quad \text{Imipenem}
\]

*first carbapenem natural product antibiotic to make it to market*

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

Karady's synthesis from Penicillin synthesis

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Prostaglandin E₁
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Mechanistic and Synthetic Studies towards the Production of Efavirenz

L-738, 372

non-nucleoside reverse transcriptase inhibitor for HIV type 1
sold in combination with tenofovir, emtricitabine: Atripla since 2006

Efavirenz

collaboration between Merck Process and Dave Collum at Cornell
Development of efficient and enantioselective acetylide addition

quinine, BuLi, THF, –25 °C
84%, 97% ee
Mechanistic and Synthetic Studies towards the Production of Efavirenz

Key Observations

2 equivalents of ephedrine and acetylride were required for complete conversion

<table>
<thead>
<tr>
<th>Pre-equilibration Temp (°C)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−40 °C</td>
<td>80 (avg)</td>
</tr>
<tr>
<td>0 °C</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

Mechanistic and Synthetic Studies towards the Production of Efavirenz

collaboration with Dave Collum at Cornell

\[
\text{propargyl} + \text{3-chloro-2-aminobenzophenone} \rightarrow \text{3-chloro-2-aminobenzophenone} \quad \text{BuLi, THF, } -40^\circ \text{C}
\]

\[ ^6\text{Li} \]
\[ ^6\text{Li}^{13}\text{C} \text{acetylide} \]
\[ ^6\text{Li}^{15}\text{N} \text{chiral amino alcohol} \]

proposed Li-tetramer


Mechanistic and Synthetic Studies towards the Production of Efavirenz

collaboration with Dave Collum at Cornell

\[ \text{H} + \text{Cl-Ph-CF}_3\text{CO} \xrightarrow{\text{BuLi, THF, } -40^\circ\text{C}} \text{Cl-Ph-CF}_3\text{COH} \]

\[ ^{6}\text{Li} \]

\[ ^{6}\text{Li}^{13}\text{C} \text{acetylides} \]

\[ ^{6}\text{Li}^{15}\text{N} \text{chiral amino alcohol} \]

acetylide delivery to re-face as predicted by tetramer structure

Mechanistic and Synthetic Studies towards the Production of Efavirenz

Mechanistic and Synthetic Studies towards the Production of 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.  
"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

Prof. David Collum

Grabowski, E. J. J. *ACS Symposium Series*, **2004**, 870 (Chemical Process Research)
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The Tibotec Synthesis of Darunavir

Addressing Resistance Towards Peptide-based HIV Protease Inhibitors

- 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

The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol

The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol

Ghosh and Merck radical cyclization approach

1. O₃, CH₂Cl₂, MeOH
   Me₂S, −78–23 °C

2. NaBH₄, EtOH, 15 °C

chiral resolution provides 95% ee of alcohol

despite expensive and unscalable radical cyclization

The Tibotec Synthesis of Darunavir

Early Synthetic Studies Towards the Preparation of the Hexahydrofuranol

Ghosh, A. K.; Leschenko, S.; Noetzel, M.


**Photochemical Conjugate Addition**

1. LAH, THF
2. 1N HCl, THF/H₂O

\[ \text{H}_2\text{SO}_4, \text{MeOH} \quad \text{then protection} \]

\[
\begin{align*}
\text{PGO} & \quad \text{75\%} \\
\text{PGO} & \quad \text{36–91\%}
\end{align*}
\]

**Difficult to Scale Photochemical Reactions**

**Reduction Provides Incorrect Diastereomer**

The Tibotec Synthesis of Darunavir

The Tibotec Synthesis of Darunavir

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

The Tibotec Synthesis of Darunavir

Completing the 6-step route to key pharmacophore

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

Horner-Wadsworth-Emmons

The Tibotec Synthesis of Darunavir

End-Game adopted from Ghosh's early synthesis

The Tibotec Synthesis of Darunavir

*End-Game adopted from Ghosh's early synthesis*

![Chemical structures](image)

**Darunavir, 12 chemical steps**

85% yield for 3 step sequence

Approved in 2006 for multiply resistance HIV 1 infections

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

Classic Syntheses in Pharmaceutical Process Research and Development
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$_{2\alpha}$

uterine contraction and bronchoconstriction

The Syntex Synthesis of Prostaglandin PGE$_1$

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

The Syntex Synthesis of Prostaglandin PGE₁

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

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

The Syntex Synthesis of Prostaglandin PGE$_1$

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

The Syntex Synthesis of Prostaglandin PGE$_1$

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

![Synthetic route of PGE$_1$](image)

<table>
<thead>
<tr>
<th>Cu(I) source</th>
<th>solvent</th>
<th>Temp (°C)</th>
<th>(% d)</th>
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<tbody>
<tr>
<td>[EtO$_3$P]$_2$CuCN</td>
<td>Et$_2$O</td>
<td>–70</td>
<td>0</td>
</tr>
<tr>
<td>Cul (0.5 equiv)</td>
<td>THF</td>
<td>–20</td>
<td>10</td>
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</table>


The Syntex Synthesis of Prostaglandin PGE\textsubscript{1}

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

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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<td>Cul (0.5 equiv)</td>
<td>THF</td>
<td>–20</td>
<td>10</td>
</tr>
<tr>
<td>none</td>
<td>Et$_2$O</td>
<td>–20</td>
<td>88</td>
</tr>
<tr>
<td>Cul</td>
<td>Et$_2$O</td>
<td>–20</td>
<td>82</td>
</tr>
<tr>
<td>Cul (0.5 equiv)</td>
<td>Et$_2$O</td>
<td>–20</td>
<td>50</td>
</tr>
<tr>
<td>[(Bu$_3$P)Cul]$_4$</td>
<td>Et$_2$O</td>
<td>–70</td>
<td>71</td>
</tr>
<tr>
<td>none</td>
<td>Et$_2$O</td>
<td>–20</td>
<td>85</td>
</tr>
<tr>
<td>Cul</td>
<td>Et$_2$O</td>
<td>–20</td>
<td>76</td>
</tr>
<tr>
<td>Cul (0.5 equiv)</td>
<td>THF</td>
<td>–20</td>
<td>67</td>
</tr>
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</table>

The Syntex Synthesis of Prostaglandin PGE\textsubscript{1}

Rich History of Prostaglandin Synthesis and Structure Elucidation in Organic Chemistry

The Syntex Synthesis of Prostaglandin PGE₁

1. NaH, phthalic anhydride
2. 15% NaOH

1. NBS, THF aq.
2. Li₂CO₃, pyridine, 90 °C

NBS then AgClO₄
acetone aq.
40%
then resolution

The Syntex Synthesis of Prostaglandin PGE₁

1. NaH, phthalic anhydride
   PhH, DMF
   then: recrystallization

2. 15% NaOH

AcO

1. NBS, THF aq.
2. Li₂CO₃, pyridine, 90 °C

acetone aq.

NBS then AgClO₄

40%

then resolution

diastereoselective cuprate addition developed at Syntex

The Syntex Synthesis of Prostaglandin PGE$_1$

one of the shortest prostaglandin syntheses at 7 steps

elegant demonstration of atom economy in classical atom-uneconomical reaction

"green chemistry" before green chemistry was cool

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Prostaglandin E1