Selected Syntheses Discussed:

**Discodermolide**
- Novartis

**Ketorolac**
- Syntex

**Biotin**
- Tanabe Seiyaku Co.

**Cortisone**
- Merck

**ERα-SERM**
- Merck

**Linezolid**
- Pharmacia

**Indinavir**
- Merck

**Zomig**
- AstraZeneca

**Lipitor**
- Pfizer

**Tamiflu**
- Hoffmann-LaRoche

**MIV-105**
- Chiron

**SB-273005**
- GlaxoSmithKline

**Claritin**
- Schering-Plough

**Amerge**
- GlaxoSmithKline

**Clarinex**
- Schering-Plough
Selected Syntheses Not Discussed:

- **Ecteinascidin 743**
  - Corey

- **Indoxacarb**
  - DuPont

- **Prozac**
  - Eli Lilly

- **Thienamycin**
  - Merck

- **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 buried 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, Streeker reaction, Moffit oxidation, Fukuyama coupling, Wohl-Zeigler bromination
(-)-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:
   c. Myles, JOC 1997, 62, 6098
   d. Marshall, JOC 1998, 63, 7885
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."
Richter

Masterpieces in Process Chemistry 11/3/04
Group Meeting

PMBO Me Me NMeOMe

\[ \text{Me Me} \]

TBSOTf, 2,6-Lut., Tol., 0 °C 90% [Chromatographic purification – 12 kg]

PMBO Me Me NMeOMe

\[ \text{Me Me} \]

Red-Al, Tol., –20 °C 68% [DIBAL-H reduction worked but –78 °C was unacceptable] [Chromatography required]

PMBO Me Me NMeOMe

\[ \text{Me Me} \]

i. TBSOTf, 2,6-Lut, 100%
ii. LiBH₄, THF –30 °C to RT, 60%

OMe

85% [Crystalline]

Me Me Me Me

\[ \text{Me Me} \]

Ph₃P, I₂, imid., Tol., RT, 90% 24% overall

Me Me Me Me

\[ \text{Me Me} \]

66% overall [Chromatography Required]

PMBO Me Me NMeOMe

\[ \text{Me Me} \]

NaHMDS, THF, (15:1 cis:trans, 31%) [Chromatography required] [No larger than 2.5 kg]

NaHMDS, I₂

Ph₃P

Me Me Me Me

\[ \text{Me Me} \]

Name?

Me Me Me Me

\[ \text{Me Me} \]

Name?

Me Me Me Me

\[ \text{Me Me} \]

i. H₂, Pd/C, tBuOH
ii. TEMPO, Phl(OAc)₂

Me Me Me Me

\[ \text{Me Me} \]

i. MeMgBr
ii. SO₃, Py, DMSO

Me Me Me Me

\[ \text{Me Me} \]

[Chromatography Required]
Masterpieces in Process Chemistry

Richter

11/3/04

Group Meeting

\[
\begin{align*}
\text{i. } & \text{'BuLi, 9-MeOBBN, THF, } -78 \degree \text{C} \\
\text{ii. } & \text{Cs}_2\text{CO}_3, \text{DMF, Pd(dpff)_2Cl}_2, \text{RT}
\end{align*}
\]

\[
\begin{align*}
\text{i. } & \text{DIBAL--H, 92\%} \\
\text{ii. } & \text{SO}_3, \text{Pyr., DMSO, 93\%}
\end{align*}
\]

\[
\begin{align*}
\text{i. } & \text{CrCl}_2, \\
\text{Name?}
\end{align*}
\]

\[
\begin{align*}
\text{i. } & \text{DDQ, H}_2\text{O, 88\%} \\
\text{ii. } & \text{Phl(OAC)}_2, \text{TEMPO} \\
\text{iii. } & \text{KHMDS, 18-c-6, 76\%}
\end{align*}
\]

\[
\begin{align*}
\text{i. } & \text{CCl}_3\text{CONCO; Na}_2\text{CO}_3, \text{MeOH, 100\%} \\
\text{ii. } & \text{DIBAL--H, DCM, } -78 \degree \text{C} \\
\text{iii. } & \text{Phl(OAc)}_2, \text{TEMPO, 80\%}
\end{align*}
\]

39 steps, 17 chromatographic purifications, 20 months
7 problematic steps identified and being optimized
**EGFR Irreversible Inhibitor**

1. Treatment of solid tumors.
2. Inhibits Epidermal Growth Factor Tyrosine Kinase.

### Initial Route vs. Improved Route

**Initial Route**

```
\[
\begin{align*}
\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH} & \quad \text{F} & \quad \text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{H} & \quad \text{AcOH} & \quad \text{NH} & \quad \text{HNO}_3/\text{H}_2\text{SO}_4, 70 ^\circ\text{C}, 81\% \\
\text{F} & \quad \text{O} & \quad \text{N} & \quad \text{HOAc, 57\%} \\
\text{O}_2\text{N} & \quad \text{F} & \quad \text{F} & \quad \text{Cl}
\end{align*}
\]
```

**Problems**
- i. 65% HNO₃/H₂SO₄, 70°C, 81%
- ii. HOAc, 57%
- [Yield loss]

**Improved Route**

```
\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{Cl} \\
\text{F} & \quad \text{F} & \quad \text{N} & \quad \text{F} & \quad \text{Cl}
\end{align*}
\]
```

- Used DMF instead of HOAc for Recrystallization 74%
- [2 recrystallizations]

**Problems**
- Last step was optimizable, but for legal reasons they had to develop:
  - i. Ac₂O, 85%
  - ii. 1.5% Pt/C, H₂, THF, 99%
  - iii. TEA, THF, 0°C; NaOH, 80%
  - iv. MeSO₃H/ACOH/THF; NaOH, 90%

**Combined 3 operations**
- into one pot, 95%
- [83% after recrystallization]
- [Observed losses to dechlorination]
- 1% Pt/C, THF, H₂
- 80% from EtOH
- < 0.2% deschloro
- [Material still lost in crystallization]

**Final**
- 8 steps (3 pots)
- 55% overall yield
- produced multikilo's
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 postpartum pain.
5. 10 mg equiefficacious with acetaminophen (1 g) or acetaminophen (600 mg)/codein (60 mg) combination.

1st Generation Route

\[
\begin{align*}
\text{NCS, DMS, DCM, } & -30^\circ C, \text{ i. } 60\% \\
\text{Mechanism?} & \\
\text{NaH, DMF; } & 55^\circ C, \text{ ii. } 60\%
\end{align*}
\]

2nd Generation Route

\[
\begin{align*}
\text{Br}_2, & 0^\circ C, \text{ i. } \\
\text{DMF, } 80^\circ C, & \\
\text{MeOH, HCl, } & \text{ ii. } \\
\text{NaH, DMF, } 75^\circ C, & \text{ ii. } \\
\text{MgO, HCl, } & \text{ iii. }
\end{align*}
\]

3rd Generation Route

Beginns 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 pyroles to C–3.
3. New routes to pyrrole-2-carboxaldehydes.
4. New routes to acylpyroles.
5. Mild reduction of acylpyroles to alklypyroles.
6. Conversion of acylpyroles to acylpyrrolidines.
7. First reported intramolecular carbenoid addition to a pyrrole nucleus.
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.
1. Important in human nutrition and animal health.
2. > 80 tons produced synthetically annually.
4. For a comprehensive review of Biotin syntheses see:
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.

"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]
"With benzene, we actually considered it beneficial 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!" 

"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 difficulty won, elegant, white crystalline material subjected by pharmacists to granulation, sometimes coloration, and compression to an unnatural form."
Indinavir

1. HIV Protease Inhibitor.

![Indinavir Reaction Scheme](https://example.com/indinavir_scheme.png)
1. Hypolipidemic.
2. Number one selling drug of all time (Natural product inspired).
4. Largest competitors:

**Lipitor**

**Mevacor**

**Zocor**

**Pravacol**

**Mechanism?**
"...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.

\[ 	ext{ClH}_2\text{N} \xrightarrow{\text{i. Na}_2\text{CO}_3, \text{H}_2\text{O, EtOAc, CICO}_2\text{Bu}} \xrightarrow{\text{ii. H}_2, 5\% \text{ Pd/C, EtOAc, BuOH, 30–50 °C}} \xrightarrow{\text{iii. NaBH}_4, \text{BuOH, 35 °C}} \xrightarrow{\text{iv. NaOMe, MeOH, BuOH, 85 °C}} \text{NH}_2 \]
1. Potent inhibitor of influenza neuraminidase at nanomolar concentrations.

**Tamiflu**

- **3 steps**
  - 70–80% yield
- **5 steps**
  - 40–45% yield

i. NaN₃, NH₄Cl, DMF, 85 °C
ii. Ac₂O, Pyr. (35%)

- **2 steps**
  - 80% yield

i. Lindlar, H₂
ii. H₃PO₄

[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.]

**MIV-105**

1. Non-nucleoside reverse transcriptase inhibitor.

- **i. SOCl₂, DEA,**
  - 0 °C, 86%
- **ii. BuMgNPr₂, THF, []**
  - I₂, THF, 5 °C, 56%
- **iii. HCl, 78%**
- **iv. TsOH, EtOH, []**
  - 93%

- **i. EtCOCl, Pyr., 100%**
- **ii. AlCl₃, 88%**
- **iii. MeI, K₂CO₃, 97%**
- **iv. (CH₂OH)₂, pTSA, PhH, 86%**

**Mechanism?**

- **i. HCl, dioxane, H₂O**
- **ii. LiOH, MeOH, H₂O**
- **iii. HCl**

- **i. TEA, EtOOCOC₂H₅**
- **ii. NaN₃, []**
- **iii. H₂N-H₂PO₄**

**Name?**

- **i. BuLi, THF, −78 °C**
- **ii. ZnBr₂, −65 °C**

- **iii. Pd(OAc)₂, (ArO)₃P, −65 °C, 85%**

**Tamiflu**

35% from Shikimic acid
20% from Quinic acid

**MIV-105**

27% overall yield
**Amerge**

1. Used to treat migraine headaches.

![Amerge Reactions](image)

**Claritin and Clarinex**

1. Antihistamines.

![Claritin and Clarinex Reactions](image)

**Notes**

- Amerge 75% overall yield
- Clarinex 47% overall yield
- Claritin 52% overall yield
SB-273005

1. Vitronectin receptor antagonist.

\[
\text{HO-} \quad \text{O} \quad \text{HO} \\
\text{CHO} \quad \text{CO}_2 \text{H} \quad \text{HO}_2 \text{C} \quad \text{CO}_2 \text{H} \quad \text{HO}_2 \text{C} \quad \text{CO}_2 \text{H}
\]

- i. Br\(_2\), DCM, 65%
- ii. itaconic acid, TEA,
- \(\text{Pd(OAc)}_2\), (o-tolyl\(_3\))P, Bu\(_4\)NBr, MeCN, 80%

\[
\text{DCA, [RuCl}_2\text{(R-BINAP)}\text{]}\_2, \quad \text{TEA, H}_2\text{, 60 °C, MeOH, H}_2\text{O, 84%}
\]

\[
\text{HO-} \quad \text{O} \quad \text{HO} \\
\text{OMe} \quad \text{OMe} \quad \text{H} \quad \text{H} \quad \text{CO}_2 \text{H}
\]

- i. ZnCl\(_2\), MeCN,
- ii. NaBH(OAc)\(_3\), DMA
- iii. TFA, Tol., [], 72%

\[
\text{HO-} \quad \text{O} \quad \text{HO} \\
\text{MeO}_2 \quad \text{C} \quad \text{H} \quad \text{CO}_2 \text{Me}
\]

- i. PPh\(_3\), DIAD, TBME
- ii. LiOH, H\(_2\)O, THF, 50 °C, 66%

\[
\text{SB-273005} \quad \text{18% overall yield} \\
\text{Last Reaction = 50 kg}
\]