A Practical Synthesis of (-)-Oseltamivir

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Against Influenza

1 zanamivir (Relenza)
2 oseltamivir phosphate (Tamiflu)

- The avian H5N1 influenza shows a lethality rate of over 50%
- Three types of influenza viruses (A, B and C) have different proteins
- Inhibitors of the M2 protein (amantadine and rimantadine) show side effects
- Zanamivir causes respiratory problems in some cases
- Oseltamivir is a prodrug and acts on NA

3 shikimic acid
4 quinic acid
The First Generation Approach to Tamiflu

“The dependence on using azide chemistry to convert epoxide 6 into oseltamivir phosphate was considered a weakness in the first-generation manufacturing process”

The Second Generation Approach to Tamiflu

![Chemical reaction diagram]

- several steps require high dilution
- low yield (20%) of the enzymatic resolution step

The Third Generation Approach to Tamiflu

![Chemical reaction diagram]

- “… it still uses sodium azide.”

Corey’s Approach: The approach features a highly enantioselective and high-yielding cycloaddition promoted by a catalytic amount of oxazaborolidine.
Shibasaki’s First Approach

1. **Ph$_3$P, MeCN, 50 °C, 3h then H$_2$O, 40 °C, 2h**
   - **Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$ rt, 2h**
     - 90% (two steps)

2. **Ni(COD)$_2$ (10 mol %)**
   - COD (10 mol %)
   - TMSCN, THF
   - 60 °C, 60h
   - 1. **Boc$_2$O, DMAP**
     - MeCN, rt, 3h
   - 2. **4 M NaOH, rt, 2h**
     - 98% (two steps)

3. **LiAlH(O$^t$Bu)$_3$, THF**
   - 4 °C, 30 min (2.1 dr)
   - 2. **DEAD, Ph$_3$P, THF**
     - 3. **3-pentanol, BF$_3$OEt$_2$**
       - 30% (three steps)

4. **TFA, CH$_2$Cl$_2$, 4 °C to rt, 3h**
   - **Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$, 4 °C**
   - **Ac$_2$O, DMAP, pyr, rt, 1h**
   - 4. **4.2 M HCl-EtOH, 60 °C, 4h**
     - then H$_2$O, 4 °C, 3h
   - 5. **H$_3$PO$_4$, EtOH, cryst.**

Shibasaki’s Second Approach

Shibasaki’s Third Synthesis

**Cong and Yao’s Approach:** The synthesis is based on a ring-closing metathesis reaction, catalyzed by second-generation Ru carbene catalyst.

1. OsO₄, NMO, acetone/H₂O
2. Pd(OH)₂, H₂, MeOH, 35 °C
3. CbzCl, NaHCO₃, H₂O/EtOAc
4. TBDPSCl, imid., DCM
5. (COCl)₂, DMSO, Et₃N, -78 °C
6. Ph₃PCH₃Br, „BuLi, THF

1. MOMCl, DIPEA, CH₂Cl₂, rt
2. Grubbs II (10 mol %) CH₂Cl₂, rt


Fukuyama’s Synthesis: Retrosynthetic Analysis

\[
\begin{align*}
&\text{1} \\
&\text{2} \\
&\text{3} \\
&\text{4} \\
&\text{5} \\
&\text{6} \\
&\text{7}
\end{align*}
\]

Fukuyama’s Synthesis: The Asymmetric Diels-Alder Reaction in Action

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\begin{align*}
\text{Pyridine} & \quad \xrightarrow{\text{CbzCl, NaBH}_4} \quad \text{Cbz-Pyridine} \\
& \quad \xrightarrow{\text{MeOH, -50 °C to -35 °C, 1h}} \quad \text{Cbz-Pyridine} \\
& \quad \xrightarrow{\text{acrolein, MeCN-H}_2\text{O, rt, 12h}} \quad \text{Cbz-Pyrazolidine-CHO} \\
& \quad \xrightarrow{\text{NaClO}_2, \text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O, 2-methyl-2-butene, tBuOH-H}_2\text{O, 0 °C to rt, 1h}} \quad \text{Cbz-Pyrazolidine-COOH}
\end{align*}
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\begin{align*}
\text{Br}_2, \text{NaHCO}_3 \text{(aq)} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{rt, 26% (4 steps)}} \quad \text{Br-Pyrazolidine-COOH}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2, \text{Pd/C, Boc}_2\text{O} & \quad \xrightarrow{\text{EtOH-THF, rt, 2h, 92%}} \quad \text{Boc-Pyrazolidine-COOH}
\end{align*}
\]

\[
\begin{align*}
\text{RuO}_2 \cdot n\text{H}_2\text{O, NaIO}_4 & \quad \xrightarrow{\text{ClCH}_2\text{CH}_2\text{Cl, H}_2\text{O, 80 °C, 1.5h, 86%}} \quad \text{Boc-Pyrazolidine-COOH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_3 & \quad \xrightarrow{\text{tBuOH, THF, 0 °C, 95%}} \quad \text{Boc-Pyrazolidine-COOH}
\end{align*}
\]

Fukuyama’s synthesis: The End

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\begin{align*}
\text{Boc}_2\text{N} & \xrightarrow{\text{NaOEt}} \text{BocN} \\
\text{OMs} & \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} \text{3-pentanol} \\
& \text{et al.} \\
\end{align*}
\]

Conclusions

• inexpensive and commonly used reagents are employed
• the overall yield of lactone from benzyl chloroformate is rather low (26%)
  this intermediate can be obtained easily with no tedious purification
• the other reactions proceed in high yields
• oseltamivir phosphate is obtained in 5.6% yield from benzyl chloroformate
  by using an asymmetric DA reaction and a Hoffman rearrangement as key
  transformations
• this synthesis uses an easily available starting material compared to the
  current industrial Roche synthesis in which shikimic acid is employed as
  precursor
• this route is has great potential for tamiflu analogues syntheses