VYTORIN treats the 2 sources of cholesterol.

Your cholesterol. It comes from pizza...and your parents.

VYTORIN lowered bad cholesterol more than Lipitor or Zocor.

VYTORIN is proven to lower bad cholesterol 45% — 60% (average effect depending on dose; 52% at the usual starting dose).

Erin Milner  2005
Crimmins Group Meeting
2 Sources of Cholesterol

The first is food, the second is your body.

In humans, more than \( \frac{1}{2} \) of total body cholesterol is derived from de novo synthesis.

LDL (low-density lipoprotein):
- can build up in the walls of your arteries and form a thick, hard plaque

HDL (high-density lipoprotein):
- helps eliminate LDL
VYTORIN Lowered LDL-C by 52% With the Starting Dose

VYTORIN Provided Excellent HDL-C Efficacy vs Atorvastatin

Lowered LDL cholesterol
Lowered triglycerides

Raised HDL cholesterol

“VYTORIN was clinically proven to lower bad cholesterol more than Lipitor or Zocor alone.”

www.vytorin.com
Cholesterol Biosynthesis

Review of synthetic approaches to mevinic acids:
VYTORIN is a tablet containing two medicines

Zetia® (ezetimibe, SCH 58235)
- Selective inhibitor of cholesterol in the small intestine
- Inhibited intestinal cholesterol absorption by 54% compared with placebo.
- Cholesterol inhibition in the small intestine decreased delivery to liver
- Caused an increase in clearance of cholesterol from the blood – complementary to HMG-CoA reductase inhibitor

Zocor® (simvastatin)
- Inactive as the lactone
- Hydrolyzed to β-hydroxyacid form
- Reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate by 45% (an early step in the biosynthetic pathway for cholesterol)
- Reduces LDL and increases HDL

www.vytorin.com
Special Populations

• **Ezetimibe**
  - Plasma concentrations for patients >65 years were 2-fold higher than younger subjects
  - Plasma concentrations were 10% higher in women than in men

• **Simvastatin**
  - HMG-CoA reductase inhibitory activity was increased 45% for patients >65 years were 2-fold higher than younger subjects
Ezetimibe (Zetia®, SCH 58235)

*Chemical Process R & D
Schering-Plough Research Institute
Wu and coworkers, *JOC*, 1999, 64, 3714*
The Schering Plough Approach

(S)-hydroxy γ-lactone
Condensation reaction of a chiral dianion with an electrophile

\[
\text{LiO} \quad \text{LiO} \\
\text{O} \quad \text{O} \\
\text{RCHO} \quad 1. \text{RCHO} \\
\text{2. H}_2\text{O} \\
\text{OH} \quad \text{H} \\
\text{R} \quad \text{R} \\
\text{O} \quad \text{O} \\
\text{H} \quad \text{H} \\
\text{OH} \quad \text{OH} \\
\text{R} \quad \text{R} \\
\text{H} \quad \text{H} \\
\text{OH} \quad \text{OH} \\
\text{with or without ZnCl}_2 \\
\text{erythro (major)} \\
\text{threeo} \\
\]

Shieh and Prestwich, *JOC*, 1981, 46, 4319
Application to Imine

in the literature

natural product core
Preliminary Studies

\[ \text{LDA, } -35^\circ\text{C, THF, HMPA} \]

\[ \text{trans} \quad + \quad \text{cis} \]

\[ \boxed{\text{heat}} \]

\[ \text{trans} \quad + \quad \text{cis} \]
Metal and Temperature Effects on Diastereoselectivity

<table>
<thead>
<tr>
<th>#</th>
<th>base</th>
<th>T (°C)</th>
<th>% Conv</th>
<th>I:II</th>
<th>Trans: cis</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂Zn</td>
<td>-25</td>
<td>80</td>
<td>11:89</td>
<td>40:60</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>-25</td>
<td>99</td>
<td>73:23</td>
<td>87:13</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDA/LiHMDA</td>
<td>-25</td>
<td>65</td>
<td>86:14</td>
<td>99:1</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>-15</td>
<td>98</td>
<td>69:31</td>
<td>90:10</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>-35</td>
<td>99</td>
<td>79:21</td>
<td>90:10</td>
<td>78</td>
</tr>
</tbody>
</table>
Optimized Procedure:
1-Step Formation of trans $\beta$-lactams

1. 2.0 eq. LDA/DMF/DMPU
2. $\text{Ar}^1\text{CH}=\text{NAr}^2$
3. LiCl, -40 °C to -15 °C
70%, trans:cis = 95:5

$\text{Ar}^1 = 4$-BnOC$_6$H$_4$
$\text{Ar}^2 = 4$-FC$_6$H$_4$

DMPU: N,N-dimethyl propyl urea (lower toxicity than HMPA)
Elaborating the $\beta$-lactam Core

![Chemical structures and reactions involving $\beta$-lactam core elaboration.](image-url)
Novel 3-step 1-pot Procedure

BSU = bis-trimethylsilyl urea

Ezetimibe
Simvastatin (Zocor®)

Chemistry Research Department
Hoffmann La Roche, Inc.
Wovkulich and coworkers, JACS, 1989, 111, 2596

Review of synthetic approaches to mevinic acids:
Rosen & Heathcock, Tetrahedron, 1986, 42, 4909
Initial Discoveries

• 1976 – Isolation of competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG CoA)
  – Endo et al. at Sankyo Co. from Penicillium citrinum (ML236B)
  – Brown et al. at Beecham Pharmaceuticals from P. brevicompactum (compactin)

• 1980 – Alberts et al. at Merck, Sharp & Dohme from Aspergillus terrus (mevinolin)

• 1981 – 1st synthesis of (+)-compactin
Common HMG-CoA Reductase Inhibitors

\[
\begin{align*}
R_1 &= \text{Me}, R_2 = H, R_3 = H \text{ (mevinolin)} \\
R_1 &= \text{Me}, R_2 = H, R_3 = \text{Me} \text{ (Simvastatin)} \\
R_1 &= R_2 = H, R_3 = H \text{ (compactin)}
\end{align*}
\]
The Hoffmann La Roche Approach
Orthoester-Claisen Rearrangement

1. NaBH₄, CeCl₃, MeOH
2. O₃, MeOH, DCM, Me₂S
3. Ph₃P=CH₂, THF

75% overall yield

Orthoester-Claisen rearrangement

Corey JOC, 1976, 41, 380

Daub JOC, 1986, 51, 3402

4 step sequence

- reduced ester to alcohol
- protected as tosylate
- displaced with sodium cyanide
- converted to acid

(S)-Pulegone

Crystalline X-ray confirmed stereochemistry

Me₂C

Me

O

H₂C

Me

OH

OH
Forming the Bicyclic Structural Motif

1. Eschenmoser’s variation of the Claisen Rearrangement

2. Tandem ene reactions described by Snider
   *JOC, 1987, 52, 5419*

Single isomer
Construction of the Lactone Moiety

1. TMS, Imidazole
2. LiEt₂BH, THF
3. Swern
4. PPh₃=CHOMe, THF, Bu₄N⁺F⁻
5. HOAc, THF, H₂O
70% overall yield

Danishefsky *JACS*, 1979, 101, 6996
Setting the final Stereocenters

Structure-activity relationship of side chain ester derivatives: \( R_3 = \text{Me} \) is 2.5 times more potent than \( R_3 = \text{H} \)
Elimination and Deprotection

1. Burgess’ reagent, 62%
2. TBAF, THF, HOAc

R₁ = Me, R₂ = TBS, R₃ = H
R₁ = Me, R₂ = H, R₃ = H (mevinolin)
R₁ = Me, R₂ = H, R₃ = Me (Simvastatin)
R₁ = R₂ = H, R₃ = H (compactin)