Green Chemistry Case Studies: Presidential Green Chemistry Challenge Awards 2012 Winners

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GREEN CHEMISTRY CHALLENGE
A U.S. EPA Program

ACS Chemistry for Life®

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Case 2:
Codexis, Inc. & Dr. Yi Tang, UCLA

Winner in the Area of Greener Synthetic Pathways

CODEXIS®

Overview

Title: *An Efficient Biocatalytic Process to Manufacture Simvastatin*

Summary:

Simvastatin, a leading drug for treating high cholesterol, is manufactured from a natural product. The traditional multistep synthesis was wasteful and used large amounts of hazardous reagents. Professor Tang conceived a synthesis using an engineered enzyme and a practical low-cost feedstock. Codexis optimized both the enzyme and the chemical process. The resulting process greatly reduces hazard and waste, is cost-effective and meets the needs of customers. Some manufacturers in Europe and India use this process to make simvastatin.

Codexis Receiving EPA Presidential Green Chemistry Challenge Award

Photo Credit: Peter Cutts Photography

Motivation

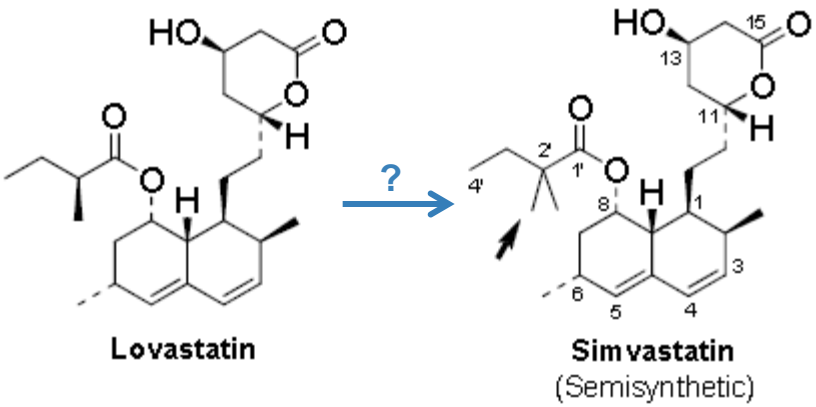
Business Drivers

- Simvastatin was originally developed by Merck under the brand name Zocor® as a cholesterol lowering drug
  - In 2005, Zocor® was Merck's best selling drug and the second-largest selling statin in the world with about $5 billion in sales
  - In 2006, Zocor® went off patent and simvastatin became the most-prescribed statin in the world
- **Why was it important to spend resources developing this technology?**
  - Simvastatin is one of the most important drugs on the market for treating cardiovascular diseases
  - In 2010, there were over 94 million prescriptions for Simvastatin
  - Codexis saw a great opportunity to reduce cost and waste to environment by reducing complexity of manufacturing process

Motivation

Innovations in Science and Engineering

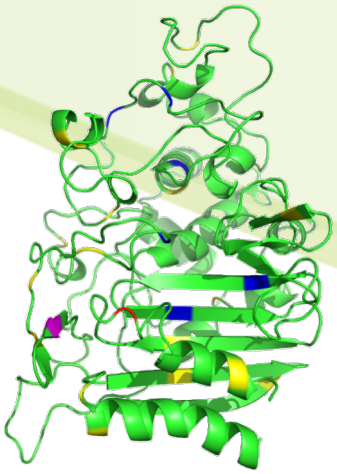
- Simvastatin is a derivative of lovastatin, a fungal natural product, and contains an additional methyl group at the C2' position of the side chain.
- This subtle structural modification makes simvastatin more potent in the reduction of total and low-density lipoprotein cholesterol (LDL-C) with decreased hepatoxicity and reduced side effects.
- Existing Technology
  - Two routes to manufacturing simvastatin:
    1) Hydrolysis/Esterification
    2) Direct Methylation
  - Disadvantages for both processes:
    - Low overall yields (<70%)
    - Utilize excess hazardous and toxic reagents
    - Require copious amounts of solvents
- **Can we do better?**



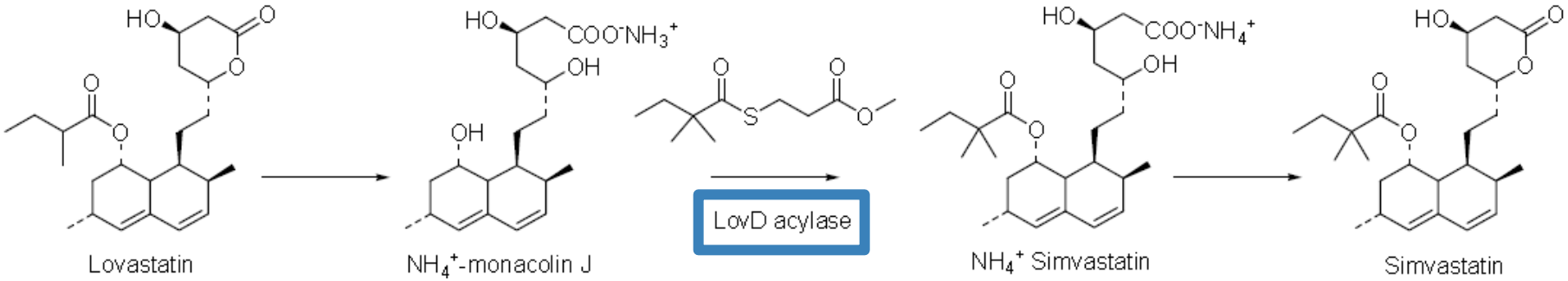
*Chemical structure of **lovastatin** (left) and its semi-synthetic derivative **simvastatin** (right) with additional methyl substituent (arrow).*

Technology Development

- **Approach:** Design a green manufacturing process for simvastatin using biocatalysis while optimizing chemical process engineering.
- The UCLA team…
  - cloned and identified the LovD enzyme for biological synthesis of lovastatin,
  - demonstrated that LovD can be used to synthesize simvastatin, and
  - identified a simple acyl donor (DMB-SMMP) that could potentially support an economic, large-scale process.

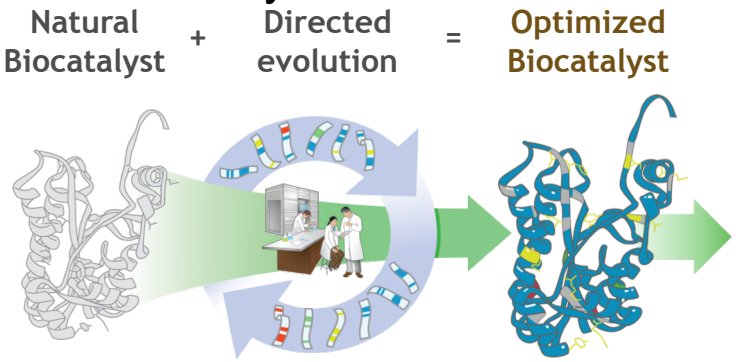


LovD acylase



Technology Development

- Codexis…
  - recognized that this basic process could be improved via its CodeEvolver™ technologies and licensed the UCLA technology,
  - improved the enzyme as well as the process chemistry to enable a large scale simvastatin manufacturing process,
  - established commercialization path via Arch Pharmalabs and a second undisclosed partner, and
  - established biocatalyst manufacture at contract manufacturer.



Business Activities

- Established commercialization path via Arch Pharmalabs and a second undisclosed partner
- Established biocatalyst manufacture at contract manufacturer
- Maintain long term relationships with several partner companies
- Partner companies come inbound seeking new technology and processes, which results in limited outbound marketing

Impact

Environmental, Health, and Safety Benefits

- Catalyst is produced efficiently from renewable feedstocks
- Reduced use of toxic and hazardous substances like tert-butyl dimethyl silane chloride, methyliodide, n-butyl lithium
- Improved energy efficiency as the reaction is run at ambient temperature and at near atmospheric pressure
- Reduction in solvent use due to the aqueous nature of the reaction conditions
- The only biproduct (methyl 3-mercaptopropionic acid) is recycled
- The major waste streams generated are biodegraded in biotreatment facilities
- Codexis' process can produce simvastatin with yields of 97%
    - Significant when compared to <70% with other manufacturing routes

Impact

Economic Benefits

- Customers have evaluated the simvastatin produced biocatalytically and confirmed that it meets their needs
- Total manufacturing costs are reduced by this new process
  - Less feedstock materials and solvents required
  - Less energy and water required during the
  - Aqueous and biodegradable waste streams

Thank You!

- The following representative was integral in the creation of this report:
  - Wes Bolsen, **Codexis, Inc.**