# Novozymes' capabilities in biocatalysis for pharmaceutical industry

## 诺维信在制药行业的生物催化解决方案

Novozymes Presentation

November 2015

- NOVOZYMES AND BIOCATALYSIS诺维信和生物催化
- CASE STUDIES实例分析

# Pharmaceuticals & fine chemicals are one of the most polluting industries
## 制药&精细化工是最污染的行业之一

**Environmental impact of some of the chemical industries**化工业对环境的若干影响

| Industries 行业 | Production Scale 生产规模 (Tons per Year)（吨/年） | E-factor E-因子 |
|---|---|---|
| Oil Refining 炼油业 | $10^6$ - $10^8$ | < 0.1 |
| Bulk Chemicals 大宗化学品业 | $10^4$ - $10^6$ | < 1 - 5 |
| Fine Chemicals Industry 精细化工业 | $10^2$ - $10^4$ | 5 - > 50 |
| Pharmaceutical Industry 制药业 | 10 - $10^3$ | 25 - >100 |

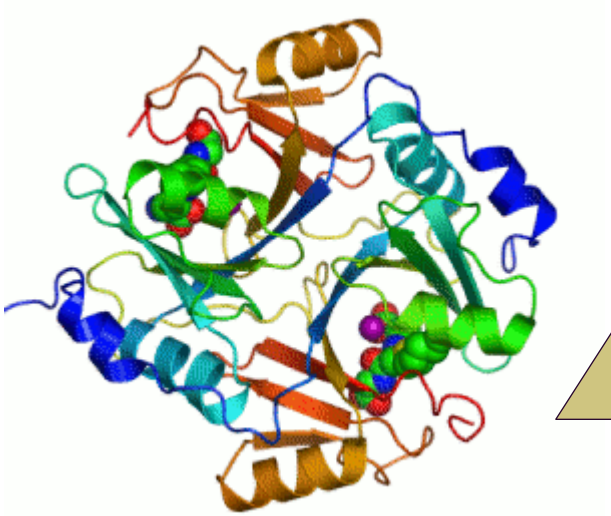
**A sustainable and greener footprint in chemical production is increasingly becoming a global need...**一条可持续的环保的化工生产道路正日益成为全球所需

**There are existing and emerging solutions to counter pollution** 这是目前新起的防止污染的解决方案

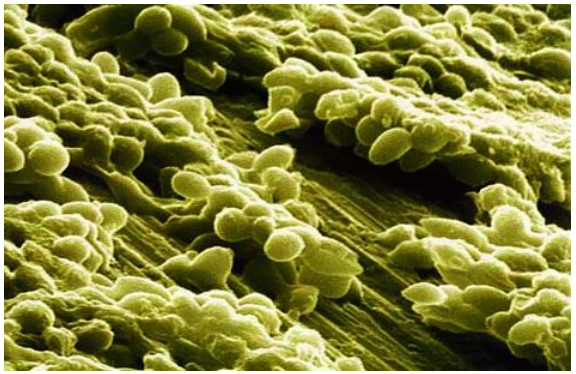
Source: R.A.Sheldon, Chem & Ind, 1992, 903 ; 1997, 12, IGCW 2011

# Biotransformation is one of the key sustainable answer to growing concerns of chemical industry
## 生物转化是化工业日益受关注的关键原因

Fermentation
发酵



Biocatalysis (Isolated Enzymes)
生物催化（隔离酶）



Whole Cells
全细胞

# There are several benefits of using enzymes over chemical reaction to produce APIs
## 生产APIs的化学反应中使用酶制剂有若干好处

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## General Advantages using Enzymes in API Manufacturing 在APIs生产过程中使用酶制剂的综合优势

- Improved Productivity 提高生产力
  - Higher Yields 更好的产量
  - Shortened synthesis route 缩短合成路线
- Greater Savings Potential 更加节约成本
  - Replaces costly chiral resolving agents 替代价格昂贵的手性拆分剂
  - Significant reduction in waste streams 有效地减少污水排放
- Greater Selectivity 更高的选择性
  - High level of Stereo-, regio-, and chemo-selectivity 高度的立体，区域和化学选择性
- Milder reaction conditions 更温和的反应条件
  - Mostly ambient reaction condition 主要是常温反应条件
- Simplified work-streams 简化工作流程
  - Simplified processing and purification 简化加工和纯化
  - Fewer byproducts, reducing impurities 更少的副产品，减少杂质

# Enzymes are already used in producing some of very important fine chemicals
## 酶制剂已经用于生产一些重要的精细化学品

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**Some examples of biocatalysis application in producing fine chemicals & API**
**生物催化在精细化学品&API生产中的应用实例**

| Compound<br>化合物 | Enzyme<br>酶制剂 | Manufacturer<br>制造商 |
|---|---|---|
| Chiral amines 手性的胺类 | *C. antarctica lipase B* | BASF |
| (R)-Mandelic acid 扁桃酸 | *(S)- or (R)-nitrilases* | BASF |
| L- or D-Amino acids 氨基酸 | *amidase* | DSM |
| Chiral alcohol 手性的乙醇 | *lipase** | DSM |
| 2-halopropionic acids 卤丙酸 | *porcine lipase* | DSM |
| (R)-Glycidyl 缩水甘油基 | *ester lipase* | DSM |
| β-Phenylalanines 苯丙氨酸 | *lipase* | Dowpharma |
| Carbocyclic nucleosides intermediate<br>碳环型核苷中间体 | *γ-lactamase* | Dowpharma |
| Protein farnesyl transferase inhibitor<br>蛋白质西基转氨酶抑制剂 | *lipase LIP-300* | Schering |
| Pregabalin 普瑞巴林 | *Lipozyme TL 100 L(Novozyme enzyme)* | Pfizer |
| Carbocyclic nucleosides intermediate<br>碳环型核苷中间体 | *Savinase (Novozyme enzyme)* | GSK/other players |

Most of these reaction are run at **industrial (multi Ton)** scale大部分反应为工业规模（万吨级）

:

# Based on the reaction types, enzymes are grouped into several classes

## 根据反应类型，酶制剂可分为若干类

Hydrolases are the most used enzyme class in biotransformation's followed by oxidoreductases 水解酶是生物转换中最常用的酶，其次是氧化还原酶

**Some key examples of enzyme classes and their applications 酶的种类和应用实例**

| Selected Reactions 参考反应 | Enzyme Class 酶种类 | EC No. | Key Applications 核心应用 |
|---|---|---|---|
| ▪ C=O and C=C reduction 降低<br>▪ **Reductive amination** of C=O 还原胺化反应<br>▪ **Oxidation** of C-H,C=C, C-N and C-O 氧化<br>▪ Cofactor reduction/oxidation 辅因子降低/氧化 | Oxidoreductase<br>氧化还原酶 | 1 | ▪ Atorvastatin Intermediate阿托法他汀中间体<br>▪ Montelukast孟鲁司特<br>▪ Sitagliptin西格列汀 |
| ▪ Transfer of functional groups such as **amino,Acyl,phosphoryl, methyl, glycosyl, nitro** & **sulphur groups** 功能基团的转化，如氨基、酰基、磷酰基、甲基、糖基、硝基&硫磺基团 | Transferase<br>转氨酶 | 2 | ▪ Cyclodextrin from Starch 淀粉提取环糊精 |
| ▪ Hydrolysis of **esters**, **amides**, l**actones**, **lactams**, **epoxides**, **nitriles** & reverse reactions 酯类，酰胺类，内酯类，内酰胺类，环氧化合物、腈类的水解反应&逆反应 | Hydrolase 水解酶 | 3 | ▪ Diltiazem Intermediate 地尔硫卓中间体<br>▪ Resolution of rac. [illegible]nylethylamine [illegible]异构体拆分 |
| ▪ Addition of small molecules to double bonds such as C=C, C=N and C=O 双键上添加小分子 | Lyase 裂解酶 (synthase) | | [illegible]酸 苹果酸<br>[illegible]termediate他汀 |
| ▪ Isomerisations such as **racemizations**, | Isomerase | | ▪ HFCS from glucose |

**Novozymes has a comprehensive Lipase/Protease/Amylase portfolio诺维信拥有广泛的脂肪酶/蛋白酶/淀粉酶**

Source:

# Novozymes has one of the most comprehensive biocatalysis enzyme portfolio
## 诺维信拥有最广泛的生物催化酶组合


- Lipases 脂肪酶
- Proteases 蛋白酶
- Esterases/cutinases 酯酶
- Oxido-reductases; 氧化还原酶
  - laccases, 漆酶
  - peroxidases, 氧化物酶
  - Chloroperoxidase 氯化物过氧化酶
- Amylolytic enzymes 淀粉酶

# Novozym 435- is the industry gold standard in lipases
## NOVOZYM 435-是脂肪酶的行业黄金标准

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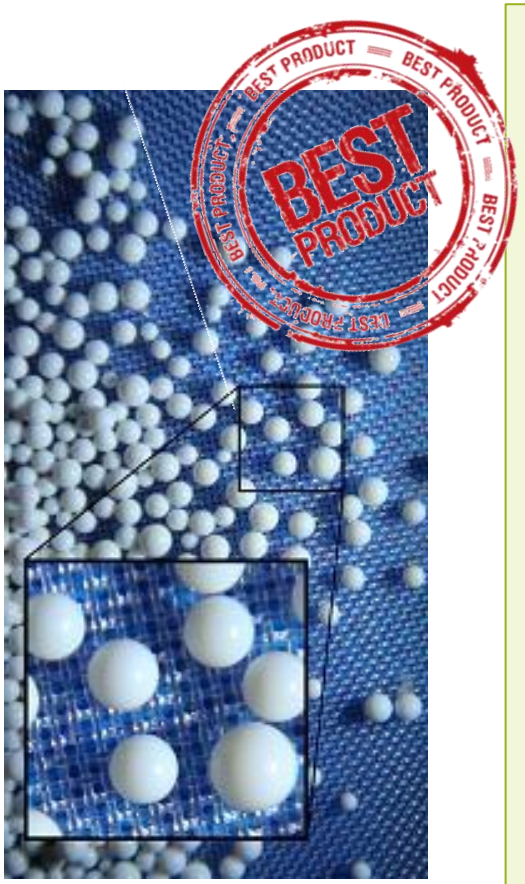
**Novozym 435 is CALBL immobilized on a polymer support**
**Novozym 435 是将CALBL固定于聚合物载体上**




**Key Advantages of Novozym 435 主要优势**

- Mild and selective on multi-functional substrates 温和和选择性的多功能底物
- Active both in bulk liquid substances and organic co-solvents 在散装液体底物和有机共溶剂均保持活跃
- Functions across wide temperature range (20-110°C) 作用于宽温域
- Suitable for both stirred batch tank / Continuous fixed bed reactors适用于批次搅拌槽和连续固定床反应器
- Recycled without activity loss for 5-10 or even more times, depending on reaction conditions 根据反应条件，可回收利用5-10次，甚至更多次不失活力
- Large-scale industrial production 大规模工业化生产
- Nil residue in the final products 最终产品无残留
- Works in anhydrous conditions & so can be used for moisture sensitive substrates 脱水条件下作用&可用于湿度敏感性底物
- Can be used with metal based racemizing reagents 可与金属外消旋试剂一起使用

**Key applications of Novozym 435 主要应用**

- Dynamic kinetic resolution of **amine** coupled with metal racemising agent 动态动力学拆分金属外消旋溶剂配合的胺类
- Dynamic Kinetic resolution of **alcohols** coupled with ruthenium catalyst 动态动力学拆分钌催化剂配合的醇类
- Kinetic resolution of ***Darunavir Intermediate*** 动力学拆分地瑞纳韦中间体

# Novozymes Immobilized Lipases……
## 诺维信固定化脂肪酶

| Novozym®435 | Lipozyme®TL IM | Novozym 40086 * |
| --- | --- | --- |
| CALB enzyme adsorbed on Macroporous Acrylic Resin<br>脂肪酶B吸附于丙烯酸树脂 | TL enzyme adsorbed on Silica Gel<br>TL酶吸附于硅胶 | RM Enzyme adsorbed on Macroporous Anionic Resin<br>RM酶吸附于阴离子型树脂 |

* Previously it was "Lipozyme ® RM IM"

# We have the industry leading robust lipase portfolio
## 我们拥有行业标杆的脂肪酶组合

### CalA type of enzymes

- *candida antarctica* lipase A
  南极假丝酵母脂肪酶A
- Allows branching on C-alpha and bulky side chains on the alcohol part
  能够在C-alpha 和醇基庞大链一侧分支

**Key Applications 主要应用**

- Kinetic Resolution of 2-phenylbut-3-yn-2-ol
  动力学拆分2- 苯基丁-3炔 -2-醇 C10H10O
- Resolution of 1-methyl-1,2,3,4-tetrahydronapth-alen-1-ol
  拆分 1-甲基-1,2,3,4-四氢萘-1-醇 C11H14O
- Kinetic resolution of (-)-***Paroxetine Intermediate***
  动力学拆分帕罗西汀中间体

### CalB type of enzymes

- *candida antarctica* lipase B
  南极假丝酵母脂肪酶B
- Allows larger groups on acid part and high specificity on alcohol part 允许较大的基团结合酸根并且对醇基有特异结合

**Key Applications 主要应用**

- Kinetic resolution of ***Lotrafiban key intermediate*** 动力学拆分洛曲非班重要中间体
- Kinetic Resolution of (S)-(+)-***Citalopram* Intermediate** 动力学拆分西酞普兰中间体
- Kinetic Resolution of ***Rivastigmine Intermediate*** 动力学拆分卡巴拉汀中间体
- Kinetic resolution of ***(R,R)-Formoterol intermediate***
  动力拆分福莫特罗中间体
- Kinetic resolution of ***Ketoprofen&Flurbiprofen***

### TLL type of enzymes

- *Thermomyces lanuginosus* lipase
  细毛嗜热霉脂肪酶
- Allows larger groups on both alcohol and acid parts允许较大基团结合在醇基和酸根上

**Key Applications 主要应用**

- Kinetic Resolution by desymmetrization of CNDE-key intermediate for ***Pregabalin***
  通过CNDE重要中间体去对称化动力拆分普瑞巴林

# Some of the other important enzymes in Novozymes portfolio are the proteases- Alcalase & Savinase

## 诺维信其他重要的蛋白酶—Alcalase and savinase

### Alcalase碱性蛋白酶

- *subtilisin* based alkaline proteases
  枯草杆菌碱性蛋白酶
- Available as liquid formulations Alcalase 2.4LFG & Alcalase 2.5L
  有液体剂型Alcalase 2.4 L FG 和 Alcalase 2.5L

**Key applications** 主要应用

- Dynamic kinetic resolution of protected Amino acids eg. DKR of ***Benzylated Tyrosine***
  动力学拆分保护氨基酸　如苄化酪氨酸

### Savinase蛋白酶

- *subtilisin* based alkaline proteases
  枯草杆菌碱性蛋白酶
- Availaible as Savinase 12T solid granulate & liquid formulation Savinase 16L
  有固体颗粒Savinase 12T & 液态剂型Savinase 16L

**Key applications**

- Kinetic resolution of vince lactam-key intermediate for ***Carbovir*** & ***Abacavir***
  动力学拆分2-氮杂双环[2.2.1]庚-5-烯-3-酮(文斯酯)——卡巴韦和阿巴卡韦的重要中间体

- NOVOZYMES AND BIOCATALYSIS诺维信和生物催化
- CASE STUDIES实例分析

# Pregabalin Biocatalytic Route
## 普瑞巴林的生物催化路径

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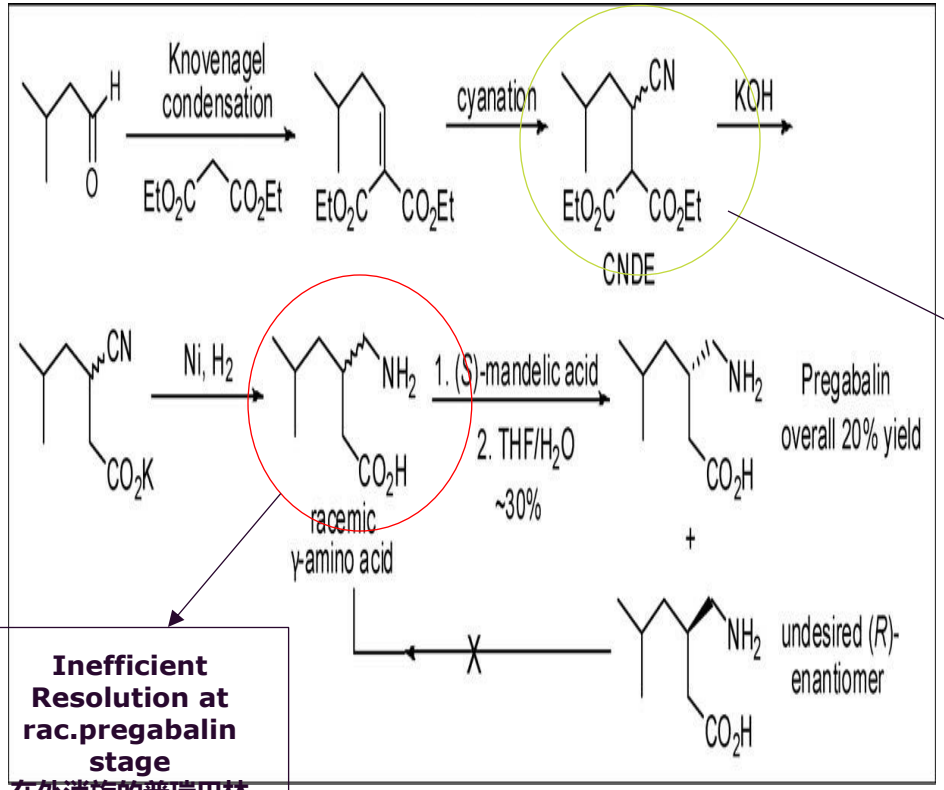
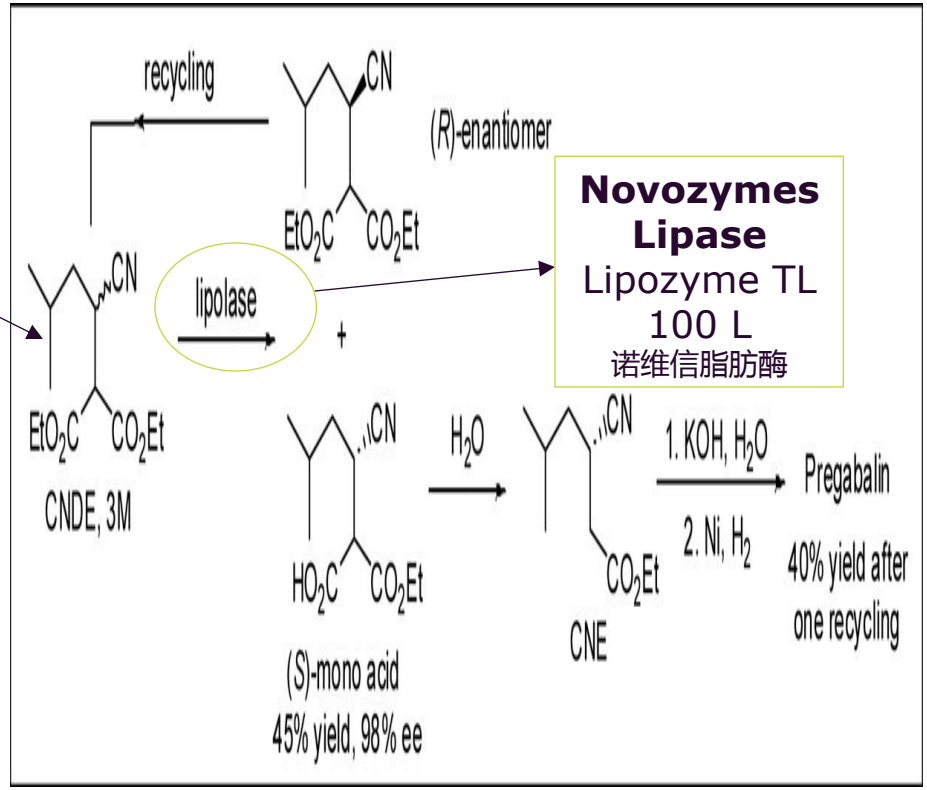
**Improvements due to replacing chemical process with chemoenzymatic reaction**
化学酶法反应替代化学过程所带来的改善

### Pregabalin Chemical synthesis 普瑞巴林的化学合成



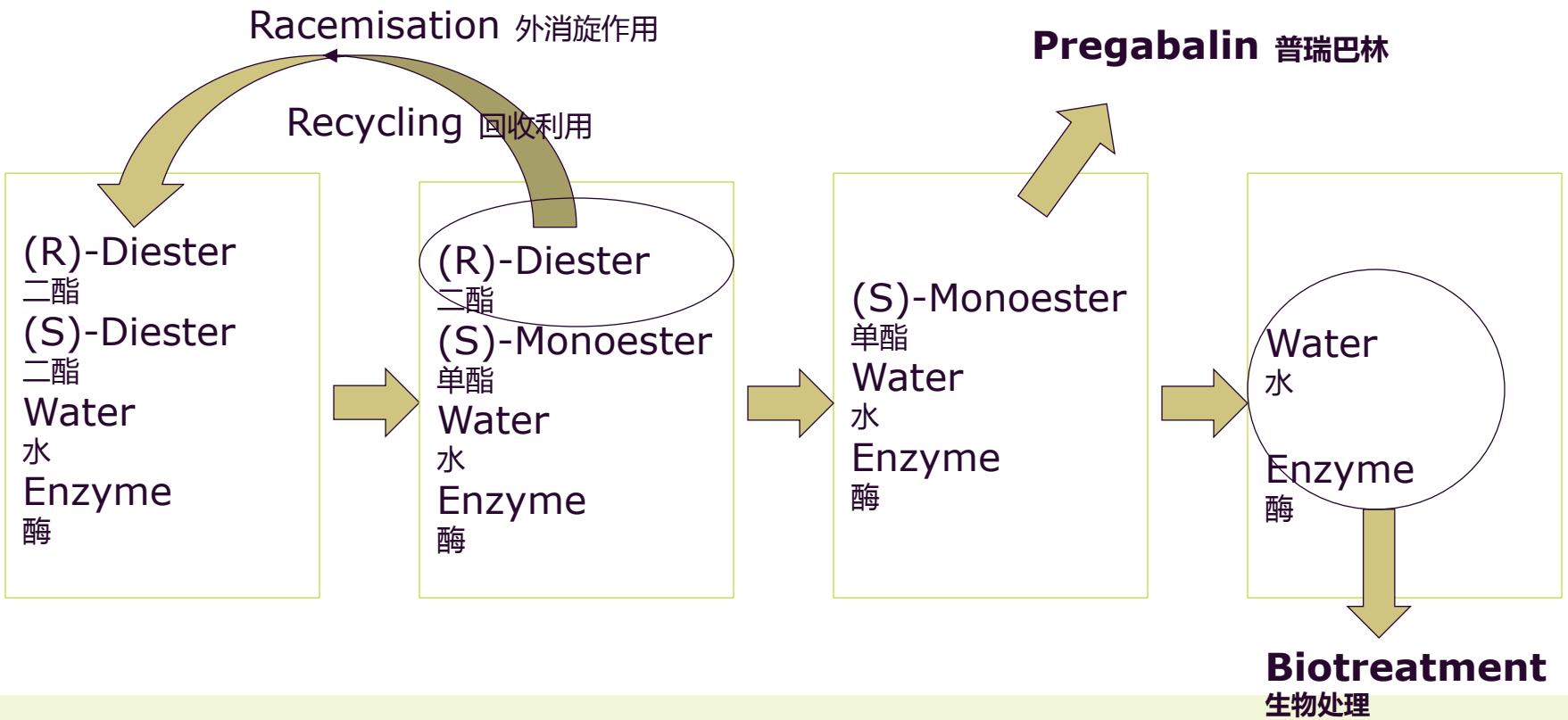

**Inefficient Resolution at rac.pregabalin stage**
**在外消旋的普瑞巴林阶段是无效拆分**

### Pregabalin Biocatalytic Route 普瑞巴林的生物催化路径




**Novozymes Lipase**
Lipozyme TL 100 L
诺维信脂肪酶

# Flow Chart of Pregabalin Process.....
## 普瑞巴林流程图




**Key Advantages of Biocatalytic Route生物催化路径的主要优势**

- Low protein Loading (0.8%) 低酶蛋白用量
- Resolution at first stage-wrong isomer can be recycled在第一阶段拆分— 错误的同分异构体可回收利用
- High throughput 高流通量
- All reactions conducted in water 所有反应在水中进行
- E-factor improved from **86** to **17** E-因子从86减少到17
- Starting material reduction by 800 Mt (cumulative) 初始物料减少800 Mt （累计的）
- Drastic reduction in solvent usage 显著减少溶剂的使用
- Mandelic acid usage-500Mt eliminated (Cumulative) 扁桃酸的使用减少 500 Mt （累计的）
- Energy usage reduced by 83% 能源消耗降低 83%

# Pregabalin Chemoenzymatic route used >5x less inputs than Chemical Route

## 化学酶法合成普瑞巴林比化学法少了多于5倍的投入量

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### Raw Material Inputs for 1000kg API Output

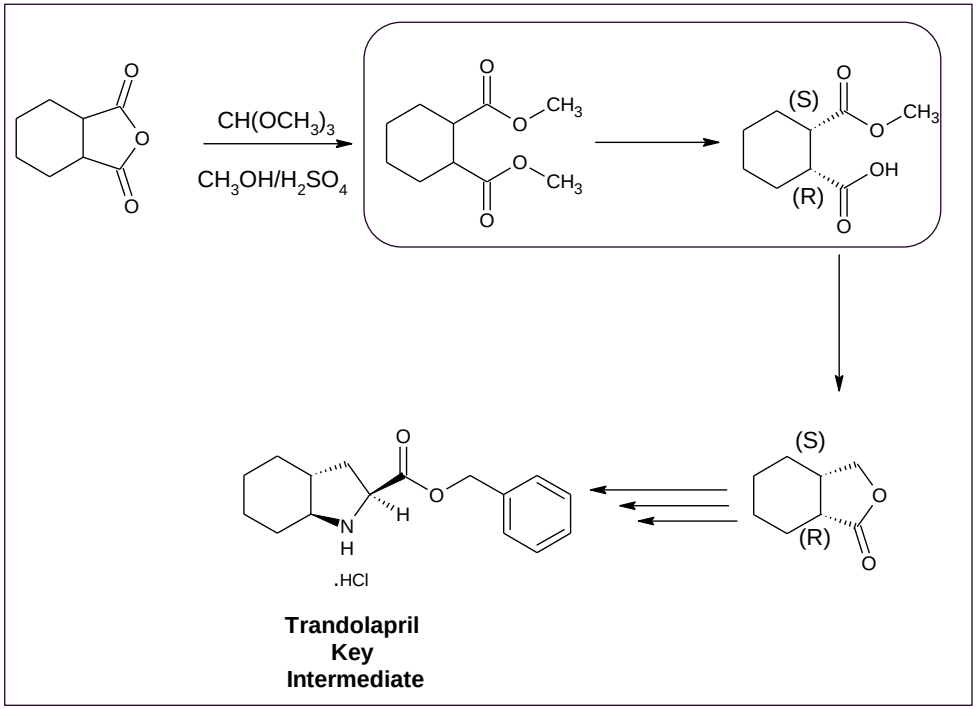
1000公斤API的原料投入量

| Inputs 投入 | Chemical Route 化学路径 Kg | Chemoenzymatic Route 化学酶法路径 Kg | Reduction 减少率 |
|---|---|---|---|
| CNDE | 6212 | 4798 | 23% |
| Enzyme | 0 | 574 | |
| S-Mandelic acid | 1135 | 0 | |
| Raney Nickel | 531 | 79.5 | 85% |
| Solvents | 50042 | 6230 | 88% |
| Total | 57920 | 11681.5 | |

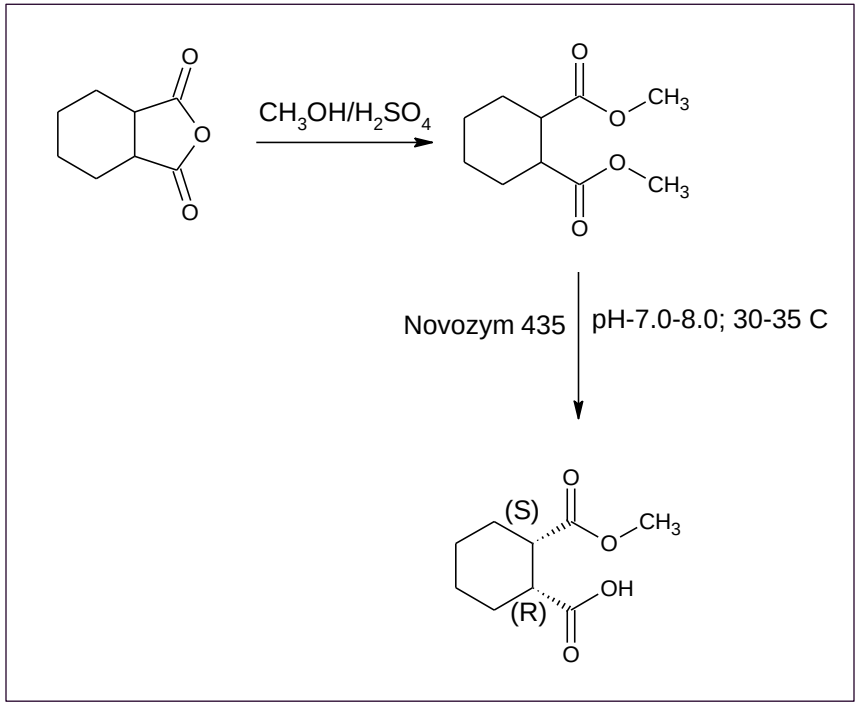
# Trandolapril Biocatalytic Route
## 群多普利的生物催化路径

**Novozym 435 gives optimum performance in stereo selective synthesis of Trandolapril key intermediate**
**Novozym 435可以高效催化群多普利重要中间体的立体选择性合成**

### Trandolapril Key Intermediate Synthesis群多普利重要中间体的合成




### Trandolapril Biocatalytic Route群多普利生物催化路径




**Key Advantages of Biocatalytic Route:** 生物催化路径的主要优势：

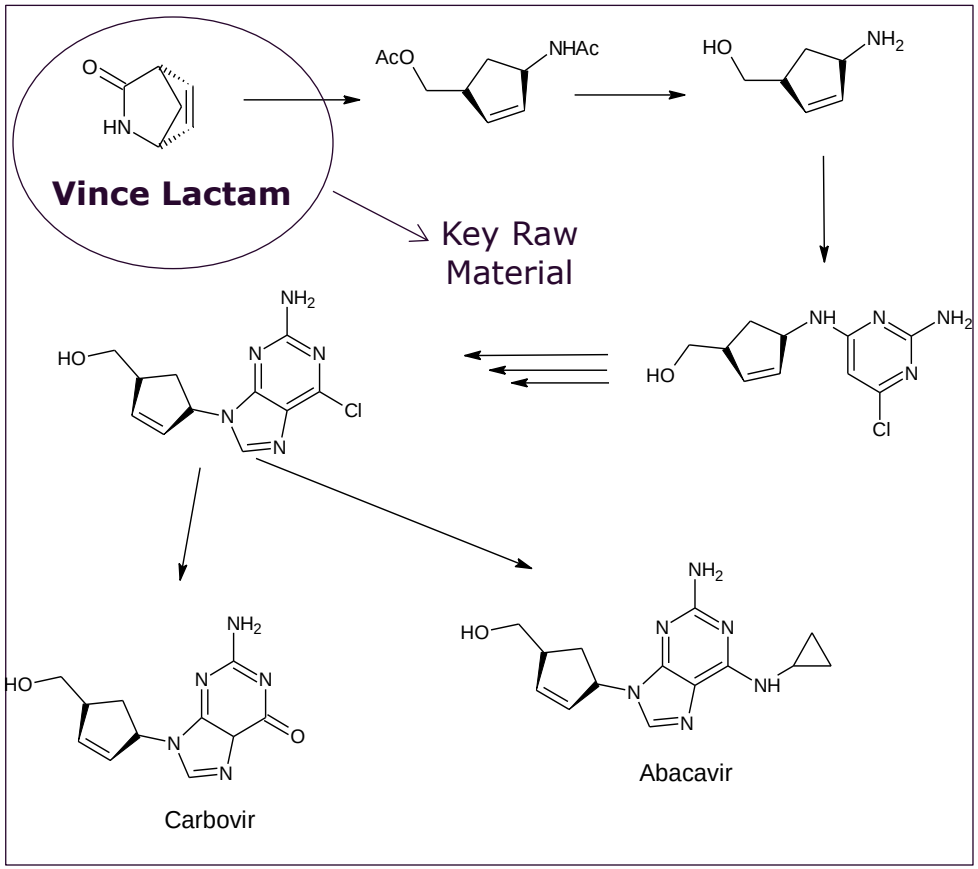
- Enzyme loading is low 低酶加量
- Substrate concentration can be as high as 100g/L 底物浓度高达100g/L
- Yield is high ~80-90% & ee> 98% 得率高达80-90% & ee>98%
- Enzyme can be recycled for approximately 5 times with out fresh loading 酶大概可以回用5次
- Reaction conditions i.e. pH & temperature is not very harsh 反应条件温和
- Reaction can be converted from batch to continuous process 反应可以由批式转为连续过程

# Vince Lactam-Carbovir & Abacavir Key Intermediate Biocatalytic Route
## VINCE LACTAM-卡巴韦及阿巴卡韦重要中间体生物催化路径

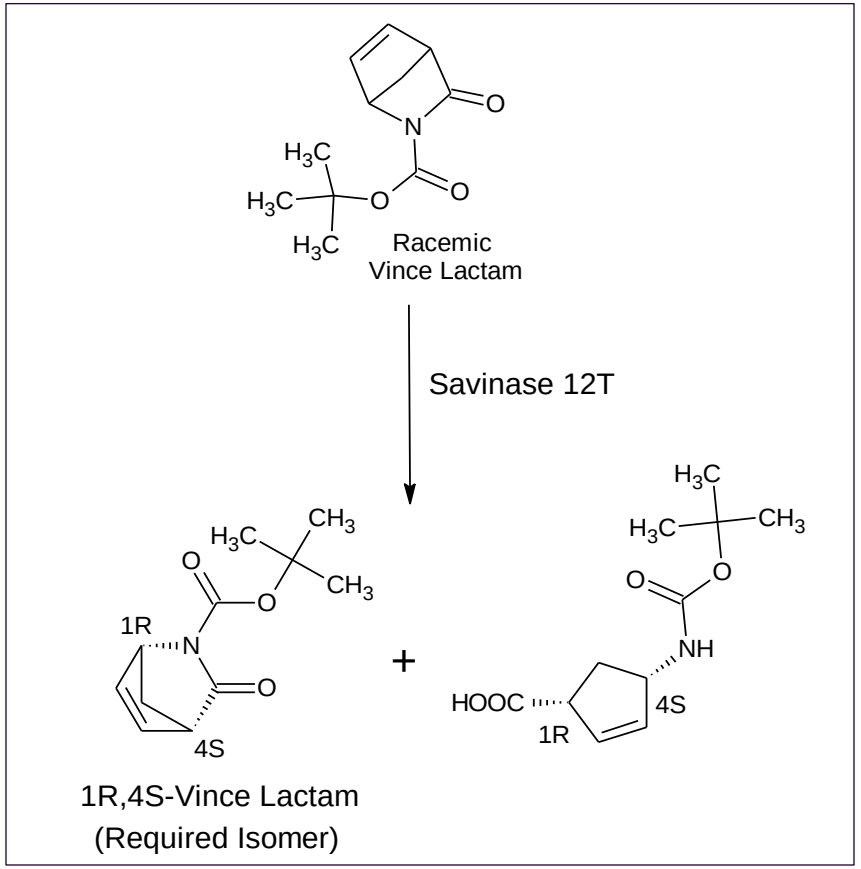
Savinase 12T is used on a commercial scale to produce Vince Lactam- Key Raw Material of Carbovir & Abacavir

**Savinase 12T用于商业规模生产Vince Lactam-卡巴韦及阿巴卡韦的重要原料**

Carbovir & Abacavir Synthesis 卡巴韦及阿巴卡韦的合成路径




Vince Lactam Biocatalytic Route Vince Lactam生物催化路径



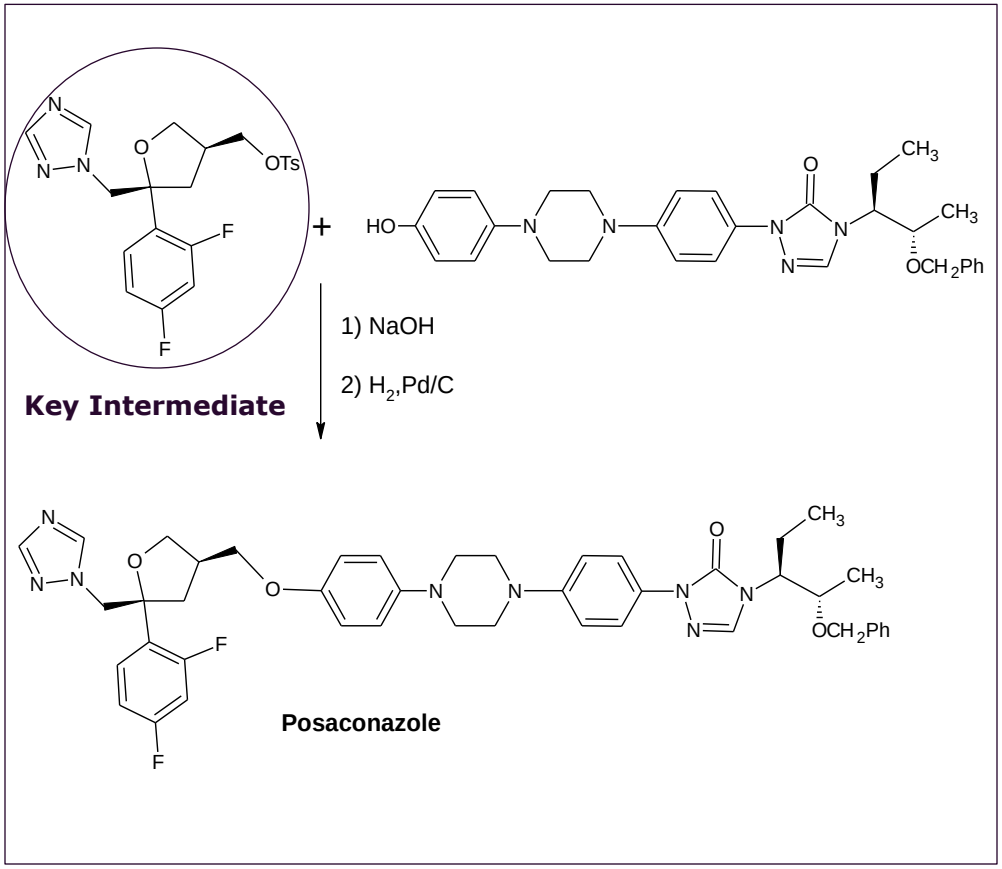

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Substrate concentration can be as high as 100g/L 底物浓度高达100g/L
- Conversion is ~50% & ee of 1R,4S Vince lactam >99% 转化率为50% & ee of 1R, 4S Vince lactam >99%
- Reaction can be carried out in a mixture of solvent & phosphate buffer 反应在有机溶剂和磷酸缓冲液中进行
- Reaction is carried out under mild & ambient conditions 反应条件温和

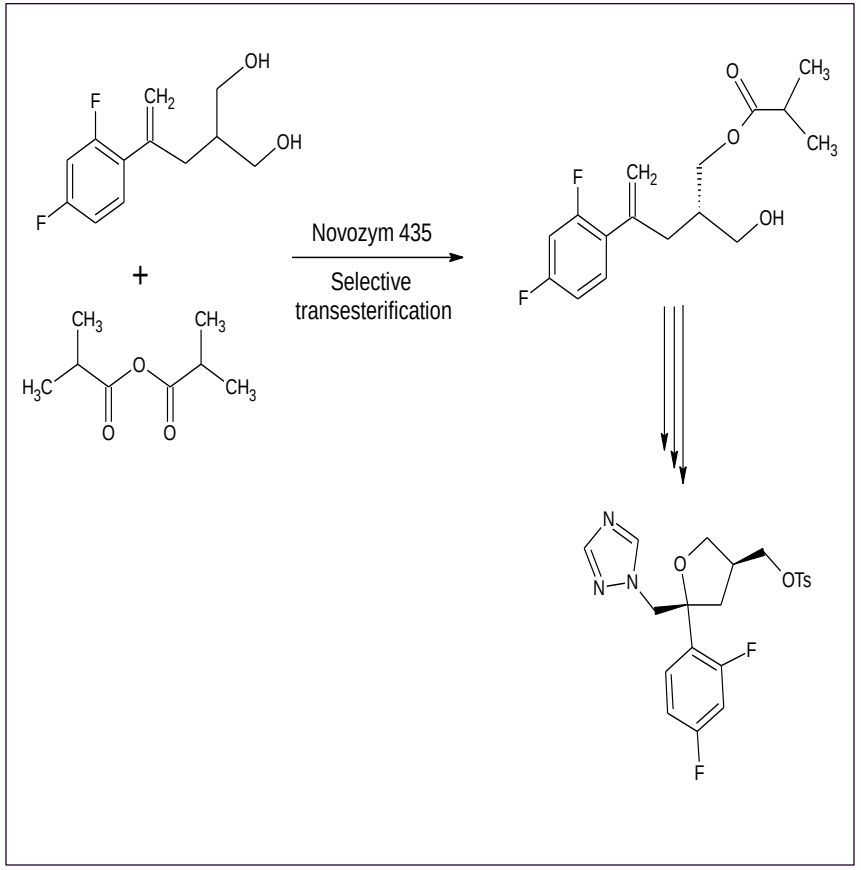
# Posaconazole Key Intermediate Biocatalytic Route
## 泊沙康唑重要中间体生物催化路径

**Novozym 435 gives optimum performance in stereoselective synthesis of Posaconazole key intermediate**
**Novozym 435可以高效催化泊沙康唑重要中间体的立体选择性合成**

Posaconazole Synthesis 泊沙康唑合成路径




Posaconazole Intermediate Biocatalytic Route 泊沙康唑中间体生物催化路径



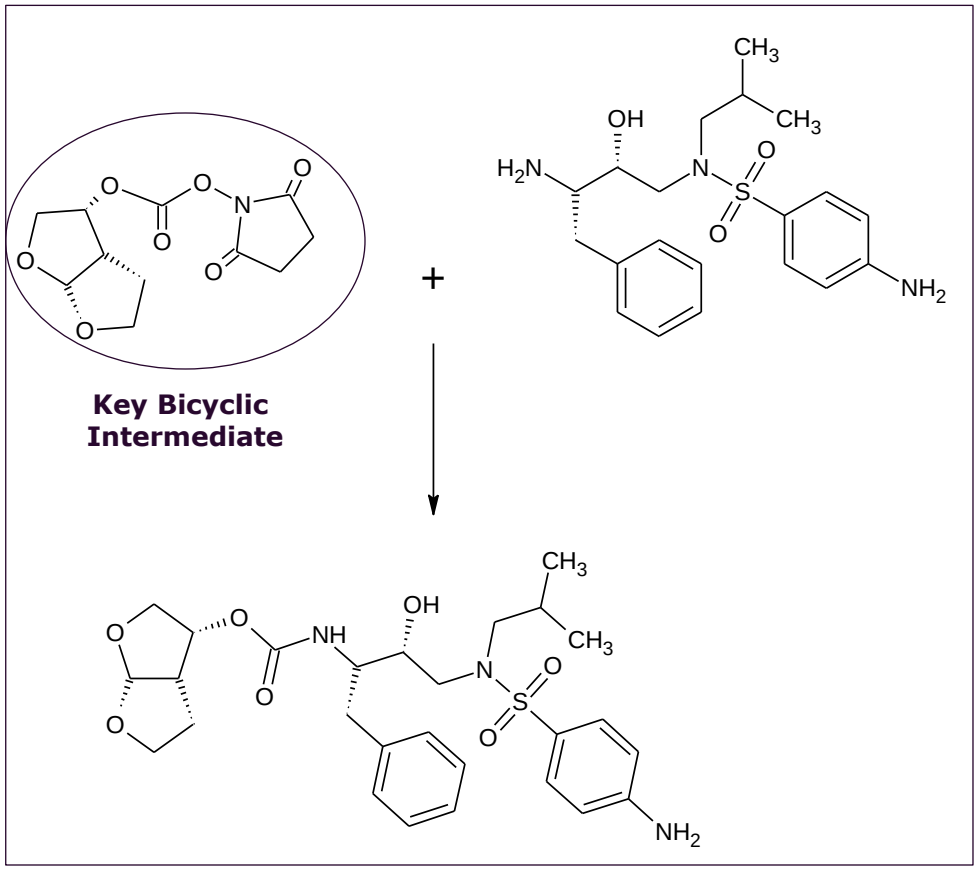

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Substrate concentration can be as high as 100g/L底物浓度高达100g/L
- Conversion is 70-80% 转化率为70-80%
- Reaction can be carried out in a non polar solvent like toluene反应可以在非极性溶剂如甲苯中进行
- Immobilized enzyme can be recycled 固定化酶可被回收再利用

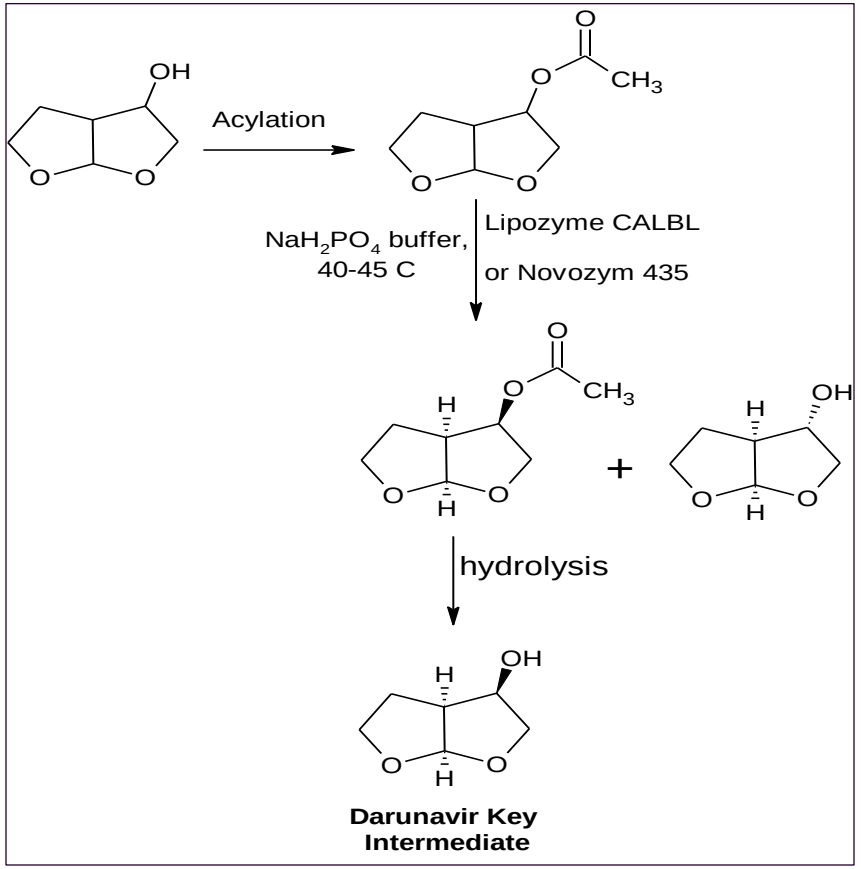
# Darunavir Key Intermediate Biocatalytic Route
# 地瑞那韦重要中间体生物催化路径

**Lipozyme CALBL is commercially used for stereoselective synthesis of key bicylcic intermediate for Darunavir**
**LipozymeCALB用于商业规模立体选择性合成地瑞那韦德重要中间体**

Darunavir Synthesis地瑞那韦合成路径




Darunavir Intermediate Biocatalytic Route地瑞那韦中间体生物催化路径



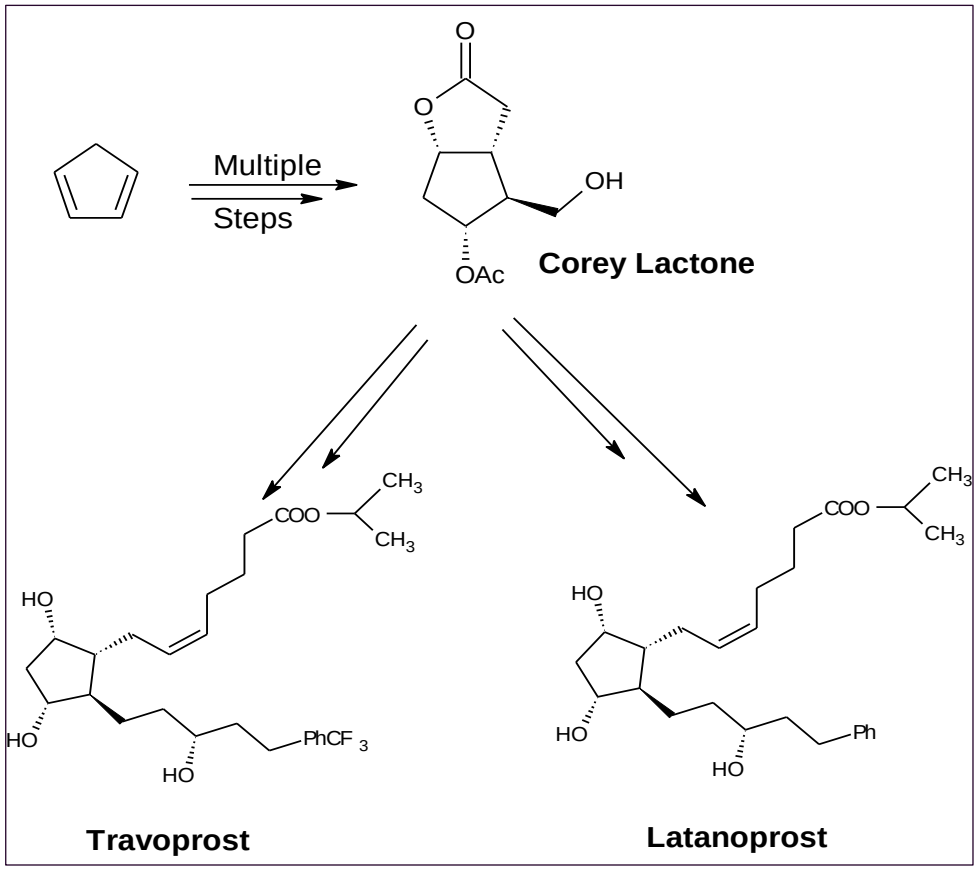

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Substrate concentration can be as high as 100g/L底物浓度高达100g/L
- Reaction can be carried out using lipozyme CALBL or Novozym 435 可以使用Lipozyme CALBL 或者Novozym 435
- Reaction can be carried out using water as a solvent 在水中进行
- Reaction is carried out under mild & ambient conditions 反应条件温和

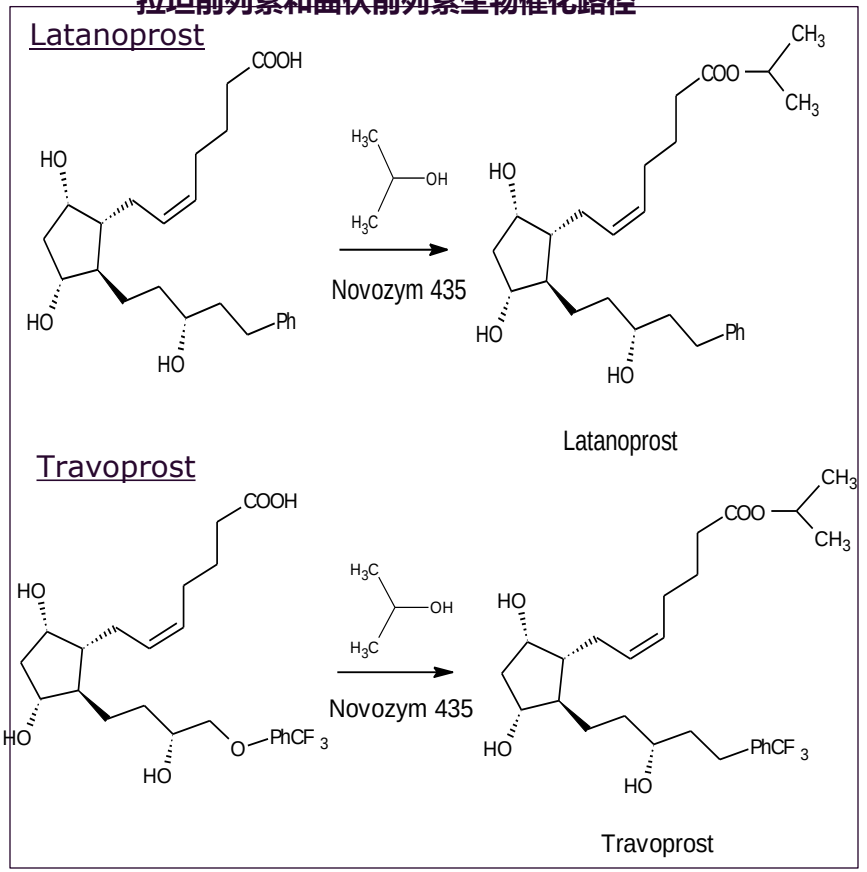
# Latanoprost & Travoprost Biocatalytic Route
# 拉坦前列素和曲伏前列素生物催化路径

**Novozym 435 is used for the key regioselective esterification step**
**Novozym 435用于关键区域选择性酯化步骤**

Latanoprost & Travoprost Synthesis拉坦前列素和曲伏前列素合成路径




Latonoprost & Travoprost Biocatalytic Route
拉坦前列素和曲伏前列素生物催化路径



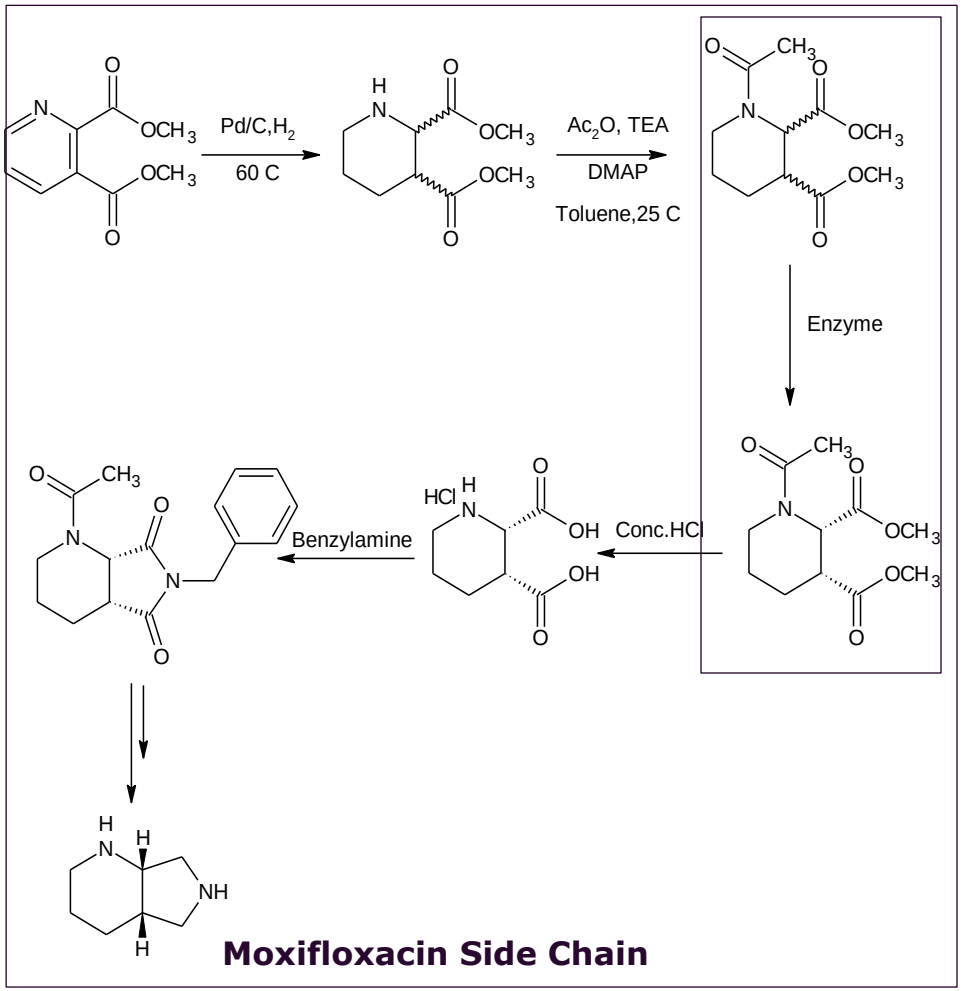

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Biocatalytic reaction is carried out at high substrate concentrations. 高底物浓度
- Reaction yields are >90% & highly regioselective. 得率>90%,高区域选择性
- Reaction can be carried out using appropriate solvent or without any solvent 使用适合的溶剂或是不用溶剂
- Reaction is carried out under mild & ambient conditions 反应条件温和

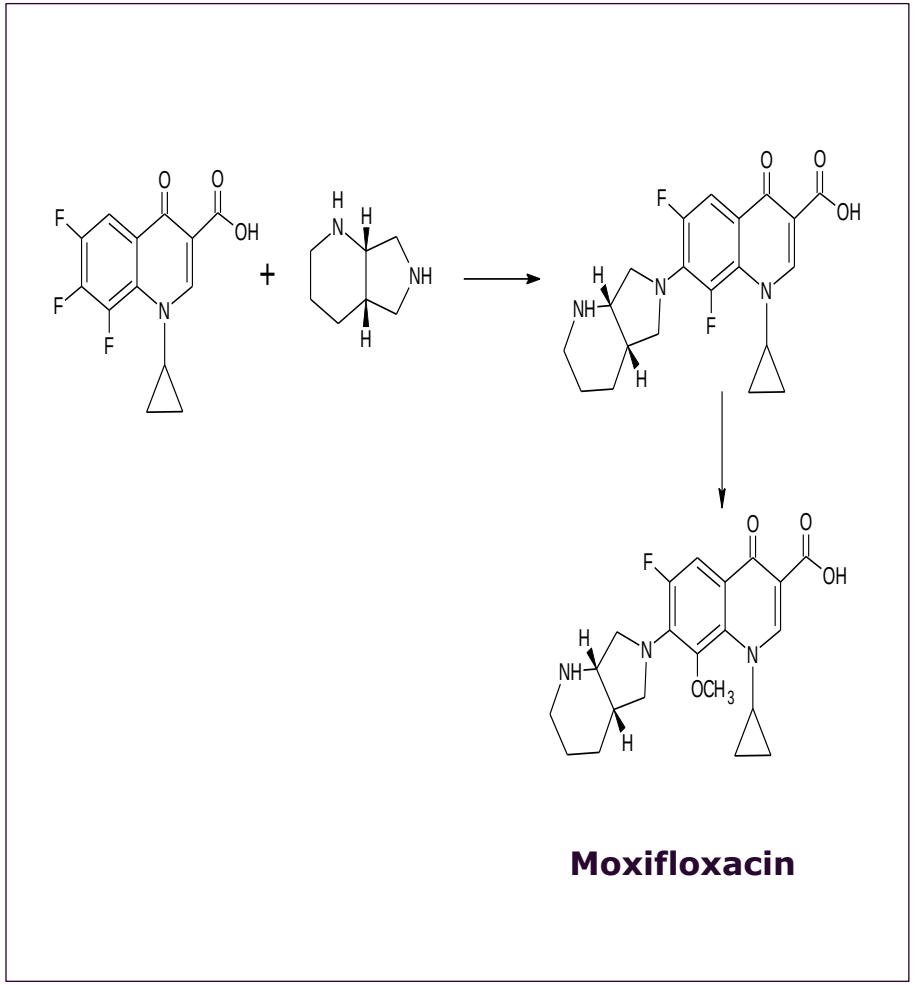
# Moxifloxacin Key Intermediate Biocatalytic Route
# 莫西沙星重要中间体生物催化路径

**Key step for moxifloxacin key intermediate manufacturing is enzymatic**
**酶可以催化莫西沙星重要中间体生产的关键步骤**

Moxifloxacin Side Chain Synthesis **莫西沙星侧链合成路径**

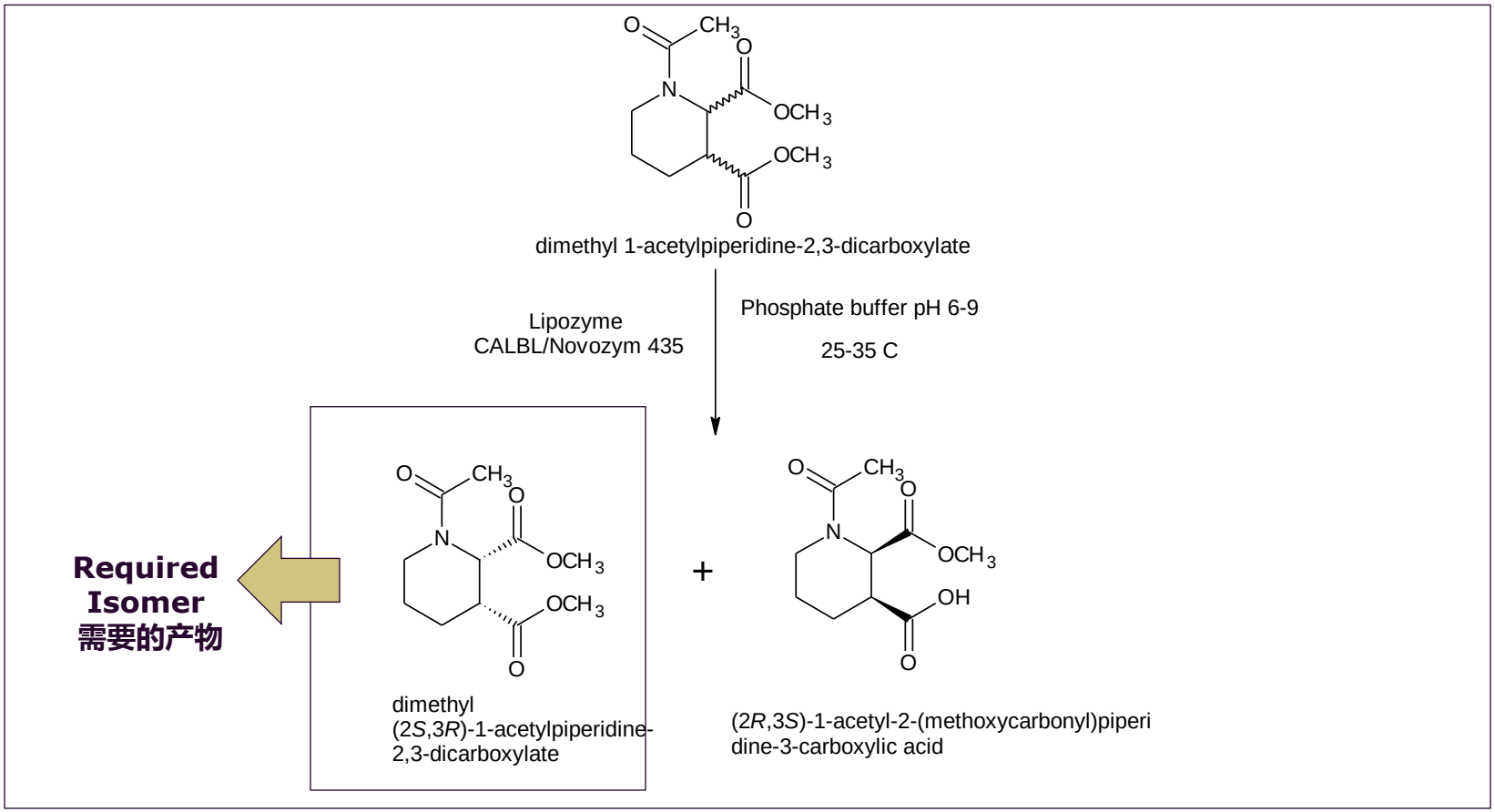



Moxifloxacin Synthesis**莫西沙星合成路径**



# Moxifloxacin Key Intermediate Biocatalytic Route
# 莫西沙星重要中间体生物催化路径

**Lipozyme CALBL or Novozym 435 can be used for desymmetrisation of racemic substrate to the required 2S,3R isomer**
**Lipozyme CALBL或者Novozym 435用于去对称化，即外消旋底物成2S，3R异构体**



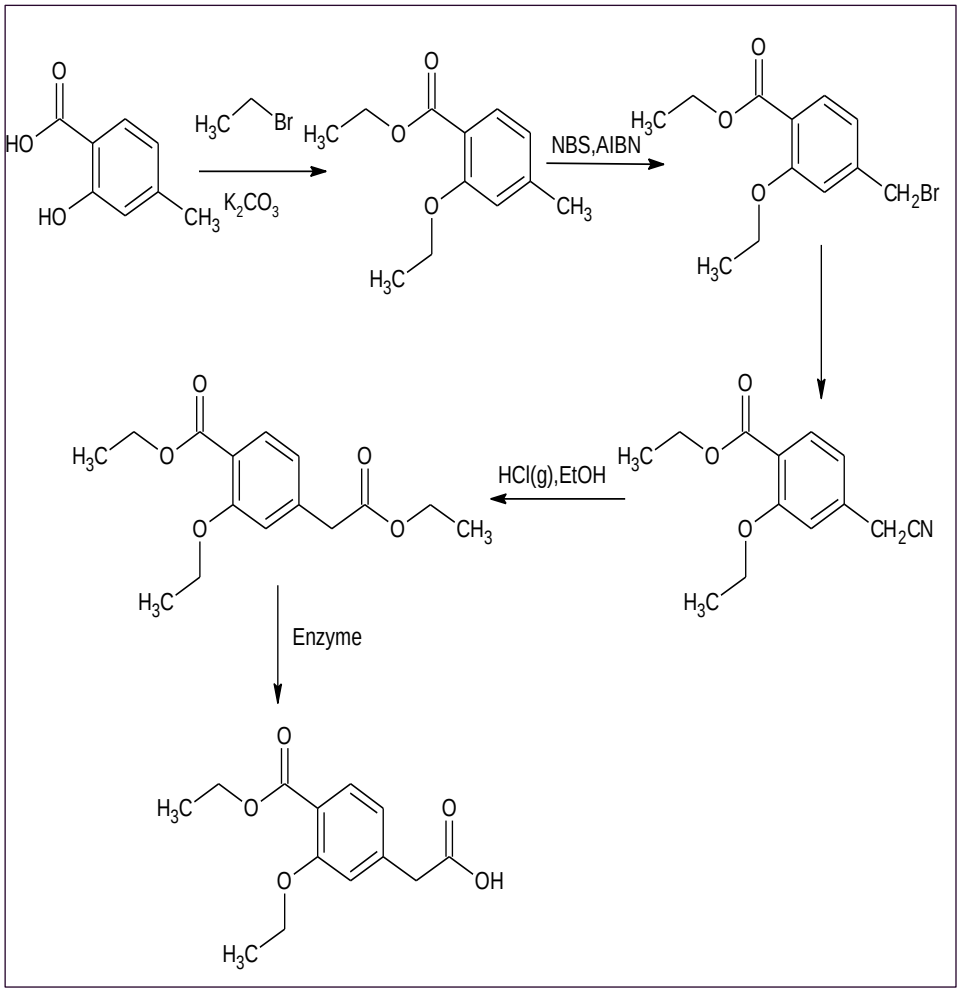

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Biocatalytic reaction is carried out at high substrate concentrations ~100g/L 底物浓度高达100g/L
- Reaction yields are >90% & highly regioselective. 得率>90%,高区域选择性
- Reaction can be carried out using appropriate solvent or without any solvent in water with appropriate buffer 可以在适合的溶剂中进行，也可以在缓冲液中进行
- Reaction is carried out under mild & ambient conditions 反应条件温和

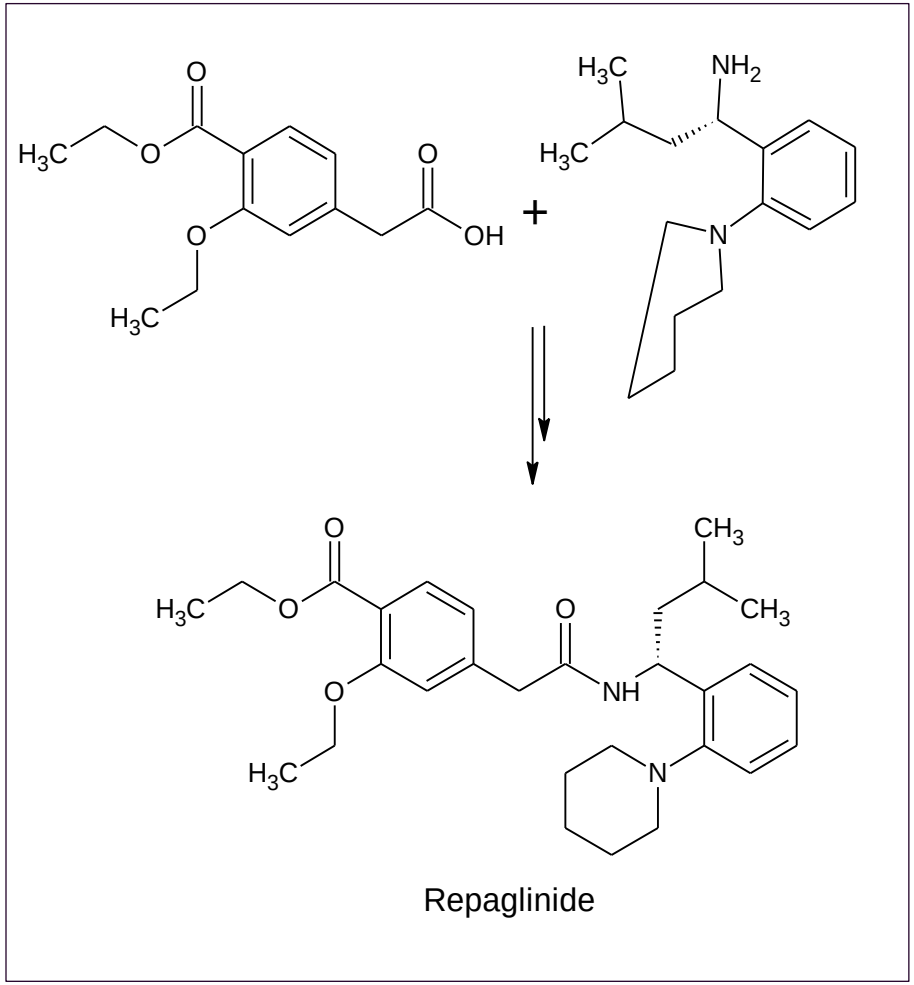
# Repaglinide Key Intermediate Biocatalytic Route
# 瑞格列奈重要中间体生物催化路径

**Key step for repaglinide key intermediate manufacturing is enzymatic**
**酶可以催化瑞格列奈重要中间体生产的关键步骤**

Repaglinide Side Chain Synthesis 瑞格列奈侧链合成路径

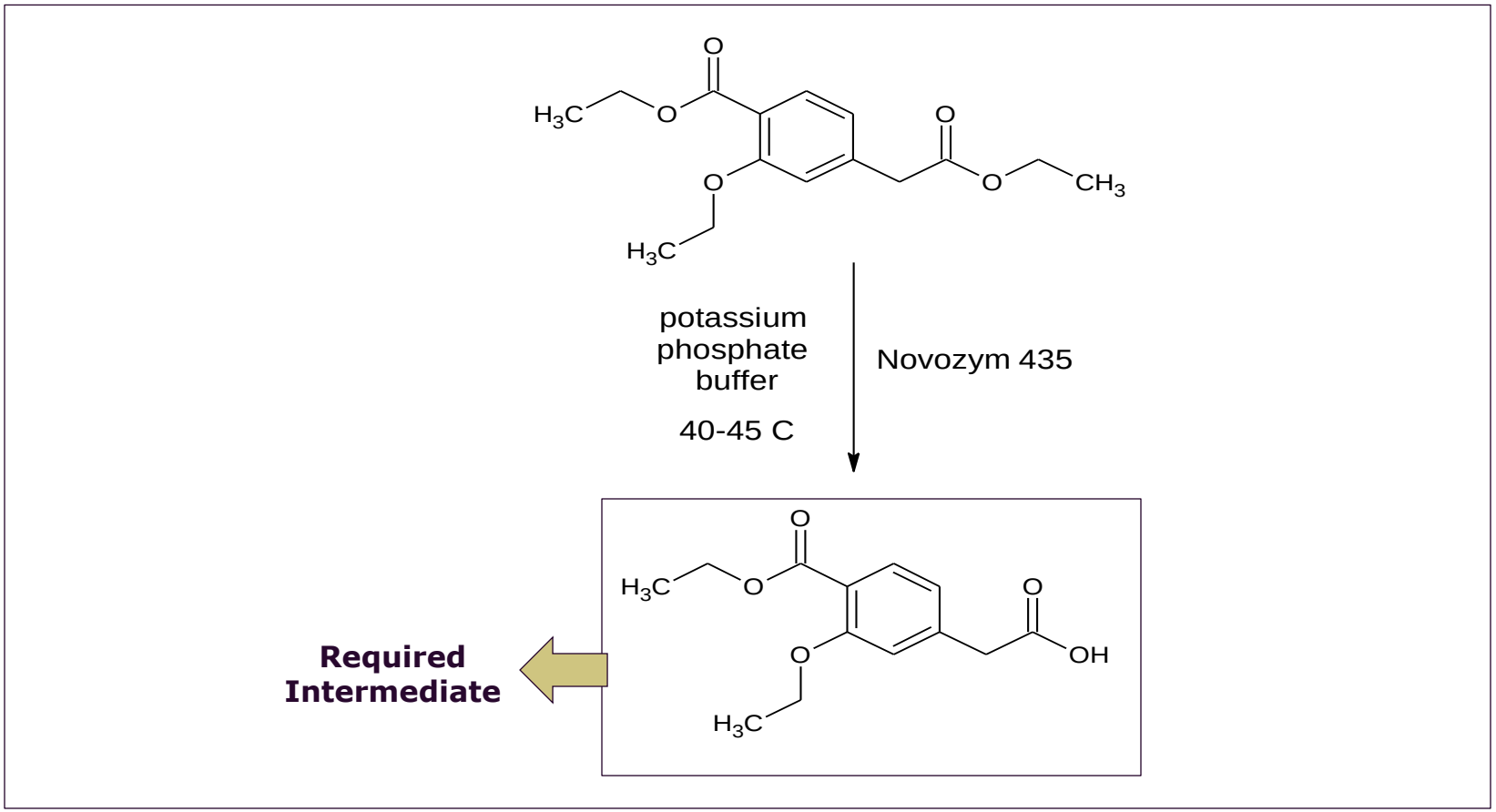



Repaglinide Synthesis 瑞格列奈合成路径



# Repaglinide Key Intermediate Biocatalytic Route
# 瑞格列奈重要中间体生物催化路径

**Novozym 435 is used for regioselective hydrolysis of diester to the required intermediate**
**Novozym 435用于区域选择性水解二元酯产生必需中间体**




**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Biocatalytic reaction is carried out at high substrate concentrations ~200g/L 底物浓度高达200g/L
- Reaction yields are ~100% & highly regioselective. 得率100%，高度区域选择性
- Reaction can be carried out using appropriate solvent or without any solvent in water with appropriate buffer 反应在适当溶剂中进行，或是在缓冲液系统中
- Reaction is carried out under mild conditions 反应条件温和

# L-Carnitine Key Intermediate Biocatalytic Route
# 左旋肉碱重要中间体生物催化路径

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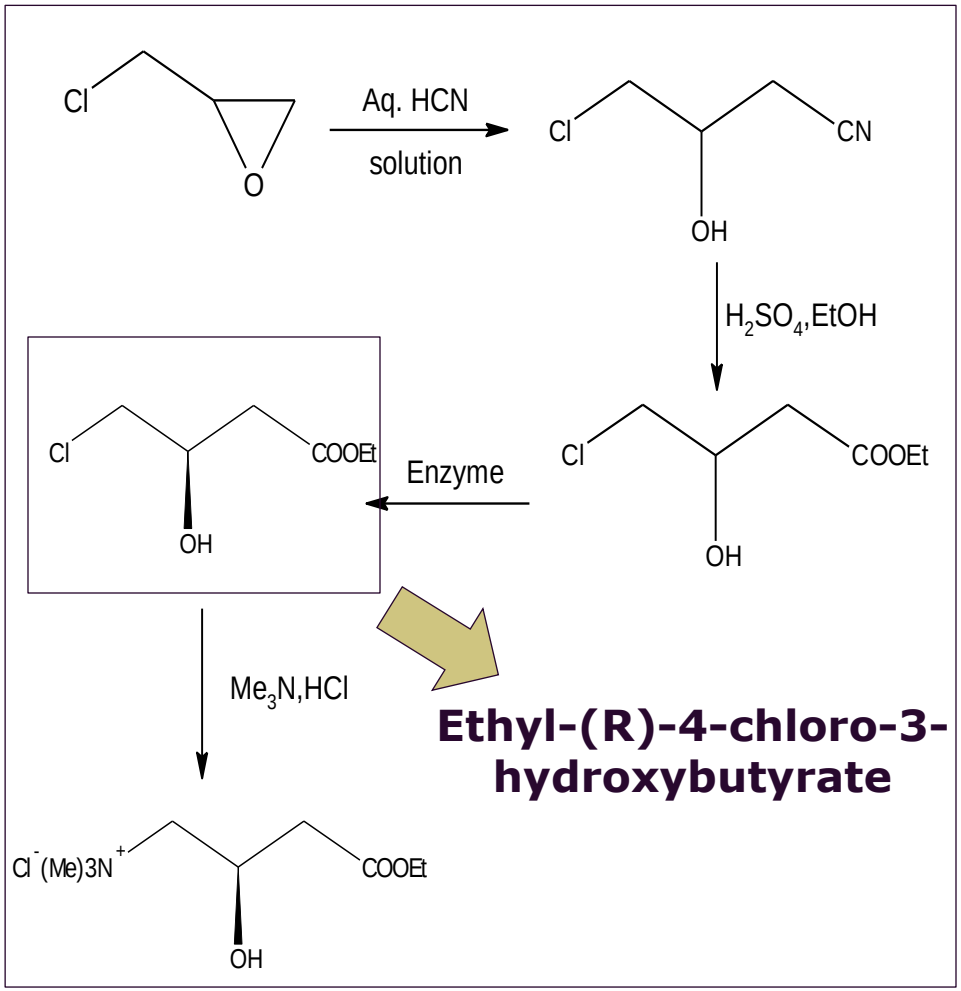
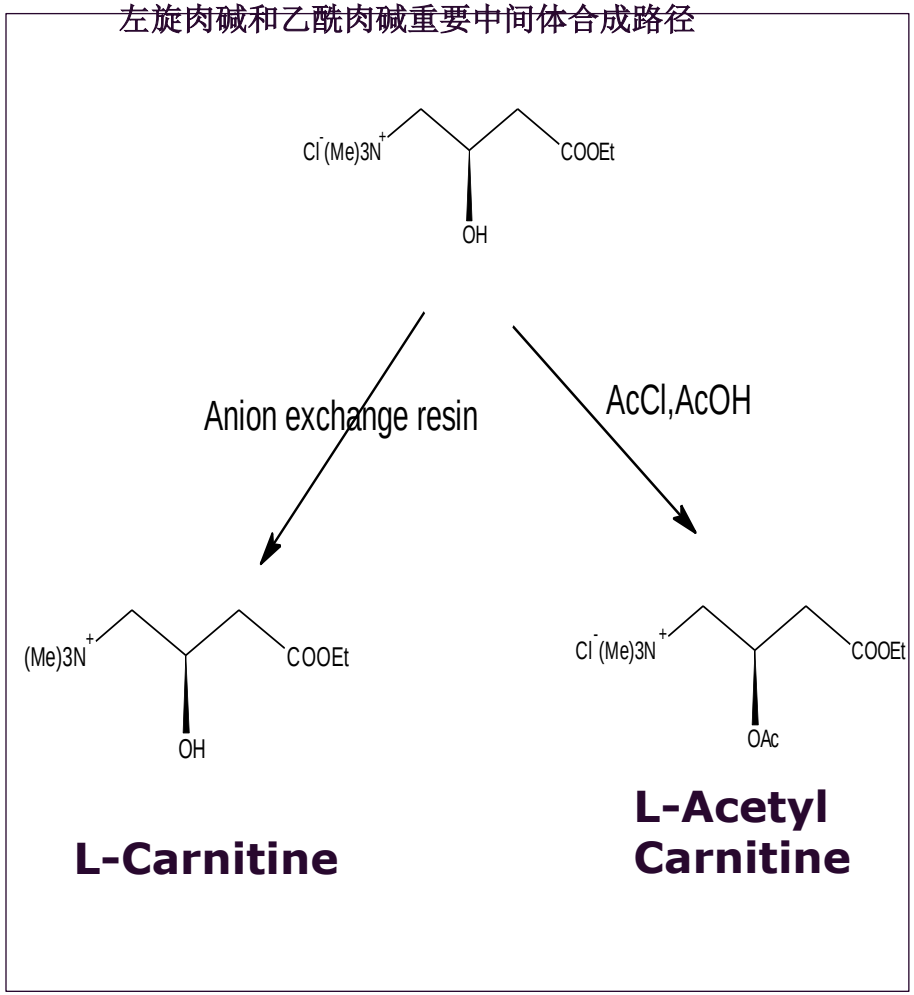
**Key step for L-Carnitine key intermediate manufacturing is enzymatic**
**酶可以催化左旋肉碱重要中间体生产的关键步骤**

L-Carnitine Key Intermediate Synthesis左旋肉碱重要中间体合成路径

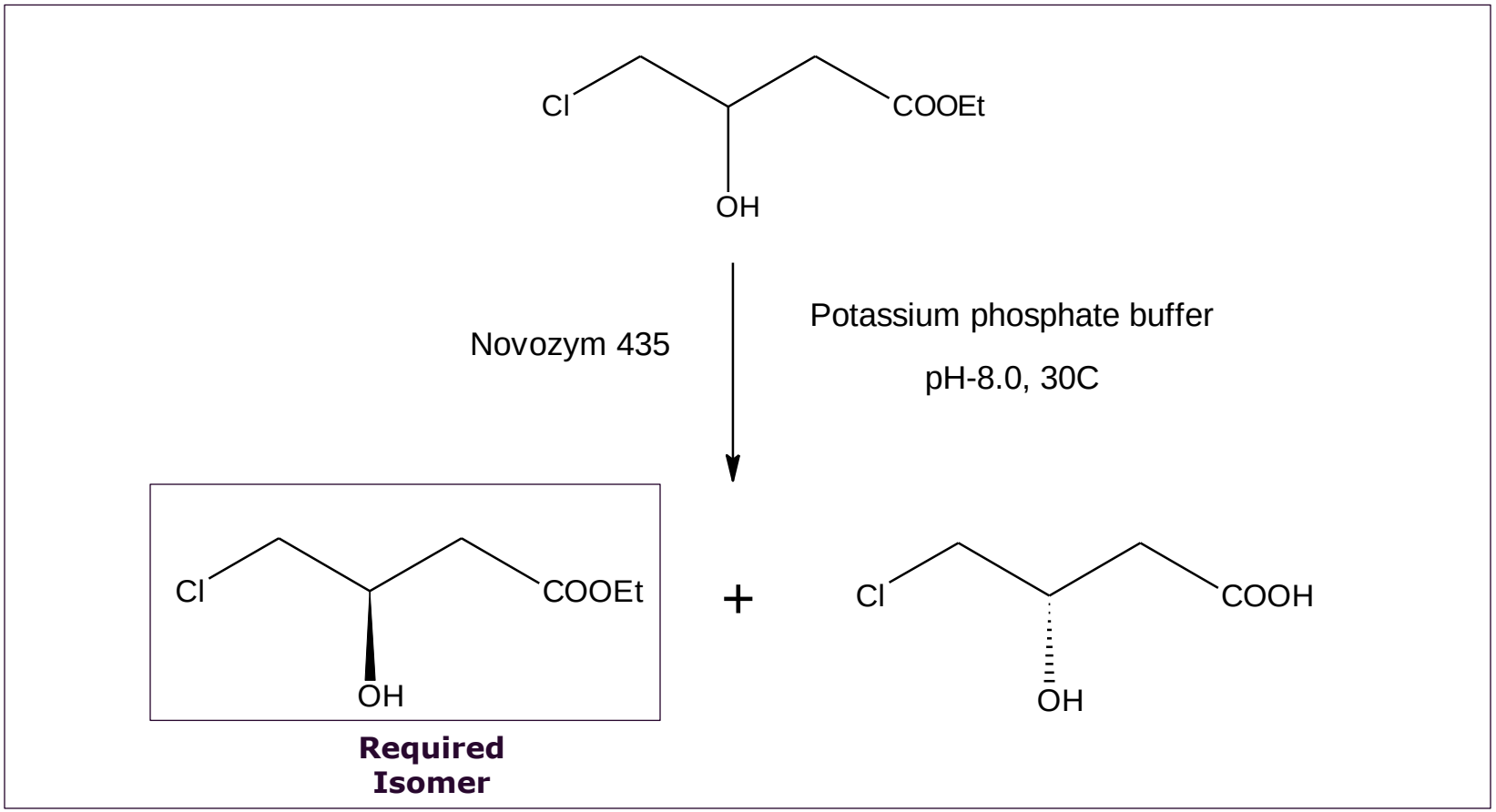



L-Carnitine & Acetyl Carnitine Synthesis
左旋肉碱和乙酰肉碱重要中间体合成路径



# L-Carnitine Key Intermediate Biocatalytic Route
# 左旋肉碱重要中间体生物催化路径

**Novozym 435 can be used for kinetic resolution of racemic ethyl-4-Chloro-3-hydroxybutyrate to ethyl-(R)-4-Chloro-3-hydroxybutyrate Novozym 435 用于动力学拆分以消旋4-氯-3-羟基丁酸乙酯成为(R) 4-氯-3-羟基丁酸乙酯**



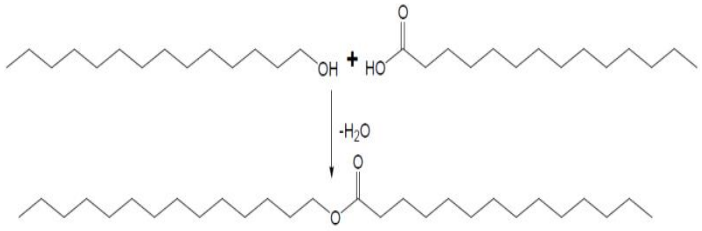

**Key Advantages of Biocatalytic Route:生物催化路径的主要优势：**

- Biocatalytic reaction is carried out at high substrate concentrations ~100g/L 底物浓度高达100g/L
- Reaction yields are ~70% of therotical yield & highly stereoselective ~99.9% ee 得率70%，高度立体选择性
- Reaction can be carried out using appropriate solvent or without any solvent in water with appropriate buffer反应在适当溶剂中进行，或是在缓冲液系统中
- Reaction is carried out under mild & ambient conditions 反应条件温和

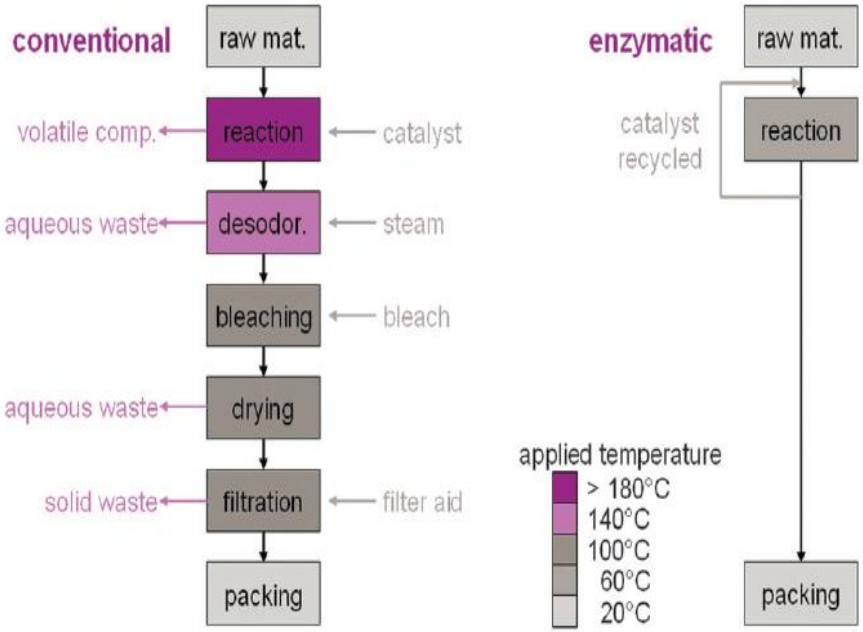
# Case story: Biocatalysis for cosmetic

## Making chemicals more efficiently

### Emollient ester








Esterification for production of cosmetic fatty acid esters.
*Chem. Soc. Rev.,* 2013, **42**, 6475--6490

**lipases** and their hydrolytic, esterifying and acylating activities show enormous potential for implementation in the production of cosmetic ingredients

# Lipase Catalysed Reactions

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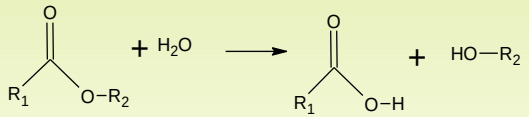
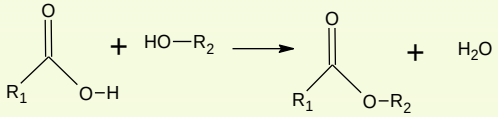
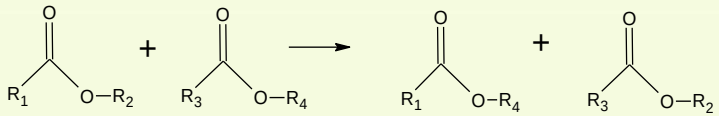
## Hydrolysis



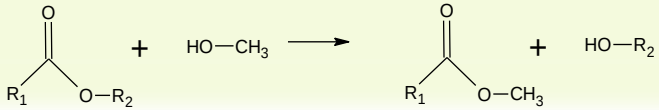

## Esterification



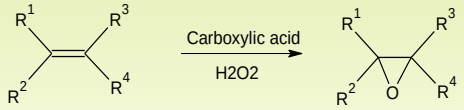

## Interesterification



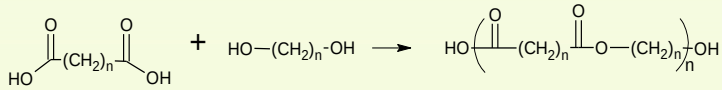

## Transesterification (e.g. methanolysis)



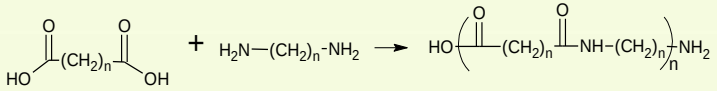

## Epoxidation



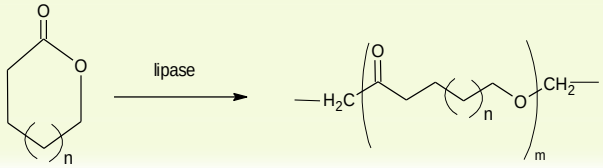

## Polycondensation




## Polycondensation




## Ring opening




# let's discuss how best we could work together

## 让我们共同探讨如何更好地合作

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