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100 years after discovery: first industrial production of PharmaPLE™ – a breakthrough for pharma applications at DSM

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DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, has successfully launched PharmaPLE™ during the Informex tradeshow in New Orleans. PharmaPLE™ is a recombinant pig liver esterase, which has been scaled and applied successfully in the synthesis of pharma intermediates. This enables a wealth of new opportunities to reduced production costs for pharma intermediates.

Oliver May, DSM's competence manager in biocatalysis comments, *“Access to recombinant pig liver esterase at any scale, without batch to batch variations, and as a non-animal derived form was a longstanding wish for many chemists. Now this wish came true. We are very pleased to have proven the real benefit of PharmaPLE™ by replacing a classical resolution process with a more economic and greener enzymatic manufacturing process for a key intermediate of a recently launched hypertension drug.”*

Background

More than 100 years ago, it was discovered that an enzyme extract from pig liver is able to hydrolyze racemic esters of mandelic acid into optically active carboxylic acids. 70 years later, the industrial potential of pig liver esterase (PLE) was proven for the synthesis of R-mevalonic acid based on a desymmetrization process. Since then, hundreds of applications have been developed using PLE. However, the enzyme has been practically banned for pharma applications after the breakout of mad cow disease in the late 1990's due to potential risks related to its animal derived origin. Now, the animal derived problem for PLE is solved.

Why is that a breakthrough?

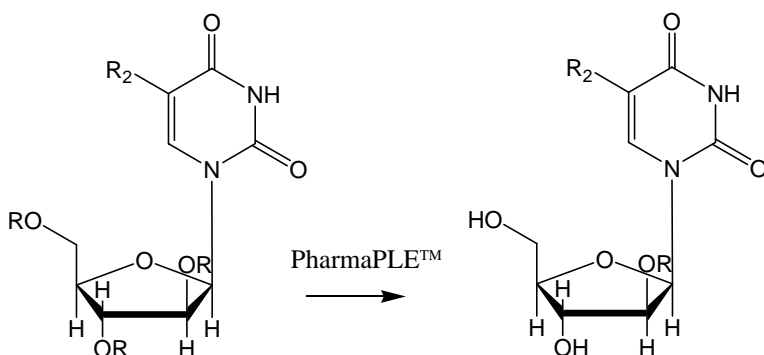
Pig liver esterase is known to be one of the most versatile biocatalyst for organic chemists. It out competes many of the large number of commercially available esterases in terms of a broad substrate spectrum and excellent enantio- and regio-selectivity. However, it is animal derived, varies significantly in quality from batch to batch and is therefore not safe and suitable for pharma applications. Together with our collaboration partner, Prof. Schwab from the Graz University of Technology (Austria), the most useful isoform of PLE, the PharmaPLE™ was identified. Based on DSM's capabilities in enzyme development and enzyme production, a highly efficient and patented microbial expression system and fermentation process was developed, which is now running at 25.000 liter scale. This makes PharmaPLE™ available at *unlimited* scale, in an *unlimited* form (reproducible, safe, non-animal derived kosher and halal) and therefore offers *unlimited* opportunities for pharma applications to our customers.

What is PharmaPLE™ good for?

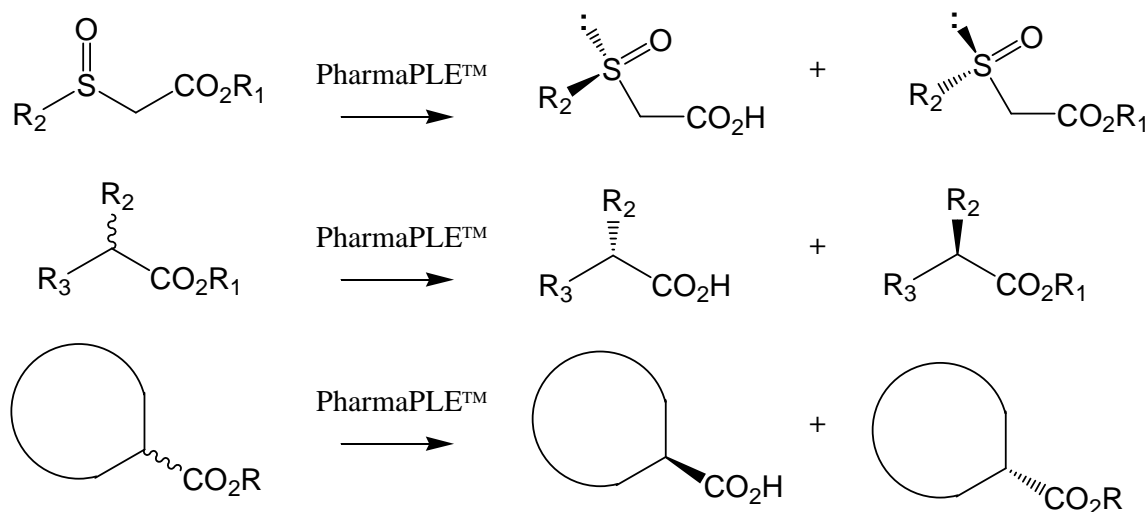
DSM is offering manufacturing solutions to complex pharma syntheses. One tool is biocatalysis, which often builds on enzyme properties like high regio-, and stereoselectivity. DSM has setup one of the most versatile enzyme collections by in-

house developments as well as by partnering with specialized biotech companies. Syntheses which require hydrolases, for example, benefit from access to more than 600 different enzymes in our collection. Nevertheless, PharmaPLE™ outperforms all of these enzymes for many reactions based on its excellent activity, stability as well as regio- and stereoselectivity. Some examples for generic structures and reactions, where PharmaPLE™ can provide the best solution, are shown below:

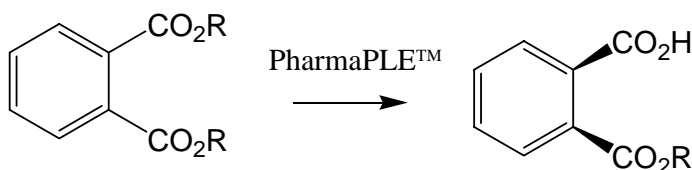
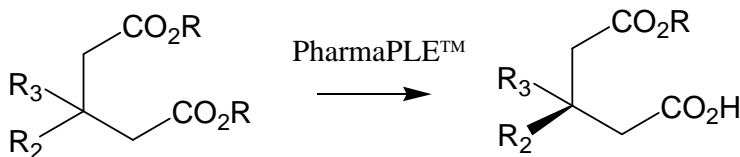
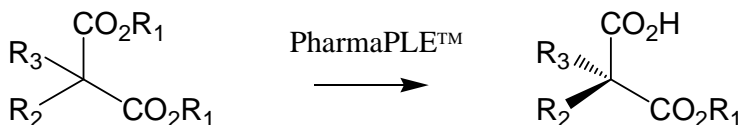
1) Highly regio-selective hydrolysis, for example:



2) Highly enantioselective resolutions, for example:



3) Highly selective desymmetrizations, for example:



Is it proven at scale?

DSM's PharmaPLE™ is, for example, used for commercial production of Synthron B at ton scale. The PharmaPLE™ based production process has substituted an established chemical process due to significant economic as well as ecologic advantages. The new enzymatic process received the DSM Gold Innovation Award in November 2007.

About DSM Pharma Chemicals

DSM Pharma Chemicals, a business unit of DSM Pharmaceutical Products, is a global provider of custom manufacturing services to the pharmaceutical industry. Our services include ResCom chemical development services, registered starting materials and intermediates, active pharmaceutical ingredients. Our menu of technologies includes biocatalysis, homogeneous catalysis and chiral technologies along with many others. Under the direction of account management teams, we're able to deliver comprehensive custom manufacturing services along spectrum of pharmaceutical companies including emerging pharmaceutical companies and large pharmaceutical companies.

About DSM Pharmaceutical Products

DSM Pharmaceutical Products is a global provider of contract manufacturing services to the pharmaceutical industry. DSM focuses the right resources on providing the highest level of service for active ingredients (API's), amino acids and derivatives, production of monoclonal antibodies, proteins, and finished dose manufacturing of solids, scheduled drugs, and liquids, aseptic liquid and lyophilized products. We'll take you there.

About DSM

DSM creates innovative products and services in Life Sciences and Materials Sciences

that contribute to the quality of life. DSM's products and services are used globally in a wide range of markets and applications, supporting a healthier, more sustainable and more enjoyable way of life. End markets include human and animal nutrition and health, personal care, pharmaceuticals, automotive, coatings and paint, electrics and electronics, life protection and housing. DSM has annual sales of almost EUR 8.8 billion and employs some 23,000 people worldwide. The company is headquartered in the Netherlands, with locations on five continents. DSM is listed on Euronext Amsterdam. More information: www.dsm.com.

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Forward-looking statements

This press release contains forward-looking statements. These statements are based on current expectations, estimates and projections of DSM management and information currently available to the company. The statements involve certain risks and uncertainties that are difficult to predict and therefore DSM does not guarantee that its expectations will be realized. Furthermore, DSM has no obligation to update the statements contained in this press release.