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MINI-REVIEW

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Biotechnological production of amino acids and derivatives: current status and prospects

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Abstract For almost 50 years now, biotechnological production processes have been used for industrial production of amino acids. Market development has been particularly dynamic for the flavor-enhancer glutamate and the animal feed amino acids L-lysine, L-threonine, and L-tryptophan, which are produced by fermentation processes using high-performance strains of *Corynebacterium glutamicum* and *Escherichia coli* from sugar sources such as molasses, sucrose, or glucose. But the market for amino acids in synthesis is also becoming increasingly important, with annual growth rates of 5–7%. The use of enzymes and whole cell biocatalysts has proven particularly valuable in production of both proteinogenic and nonproteinogenic L-amino acids, D-amino acids, and enantiomerically pure amino acid derivatives, which are of great interest as building blocks for active ingredients that are applied as pharmaceuticals, cosmetics, and agricultural products. Nutrition and health will continue to be the driving forces for exploiting the potential of microorganisms, and possibly also of suitable plants, to arrive at even more efficient processes for amino acid production.

Introduction

As the building blocks of life, amino acids have long played an important role in both human and animal nutrition and health maintenance (Bercovici and Fuller 1995). On account of its functionality and the special features arising from chirality, this class of compounds is biochemically extremely important and of great interest for the chemical industry (Leuchtenberger 1996). Of the 20 standard protein amino acids, the 9 essential amino acids-L-valine, L-leucine, L-isoleucine, L-lysine, L-threonine, L-methionine, L-histidine, L-phenylalanine, and L-tryptophan occupy a key position in that they are not synthesized in animals and humans but must be ingested with feed or food.

In terms of market volume, development over the last 20 years has been tremendously bullish in the so-called feed amino acids L-lysine, DL-methionine, L-threonine, and L-tryptophan, which constitute the largest share (56%) of the total amino acid market, estimated in 2004 at approximately US $4.5 billion (Fig. 1). Also substantial is the share of the food sector, which is determined essentially by three amino acids: L-glutamic acid in the form of the flavor-enhancer monosodium glutamate (MSG) and the amino acids L-aspartic acid and L-phenylalanine, both of which are starting materials for the peptide sweetener L-aspartyl L-phenylalanyl methyl ester (Aspartame), used, for example, in "lite" colas.

The remaining proteinogenic amino acids are required in the pharmaceutical and cosmetics industries and are also ideal raw materials for synthesis of chiral active ingredients, which in turn find application in such sectors as pharmaceuticals, cosmetics, and agriculture. According to a study by the Business Communication Company (Brown 2005), the amino acid market for synthesis applications is growing at an annual rate of 7% and is expected to reach a volume of US $1 billion in the year 2009, of which the share of amino acids for peptide sweeteners alone is expected to be more than US $400 million.

Microbial amino acid production

The rapid development of the amino acid market since the 1980s is due in no small part to major successes in cost-effective production and isolation of amino acid products. Of the four production methods for amino acids—extraction, synthesis, fermentation, and enzymatic catalysis—it is particularly the last two biotechnological processes, with

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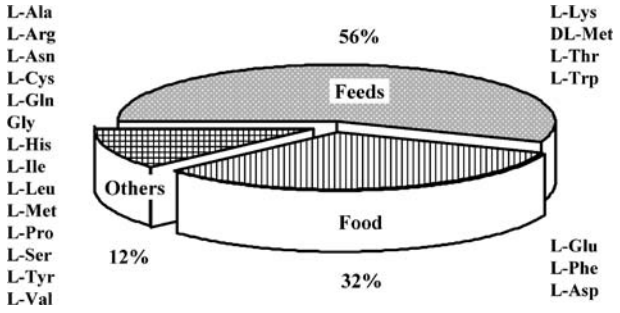

Fig. 1 Global market amino acids, 2004: US $4.5 billion

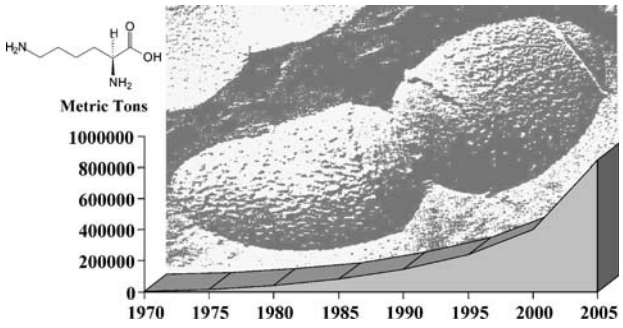

Fig. 3 Global market for L-lysine (1970–2005). The picture shows the lysine-producing mutant of *C. glutamicum*—after cell division

their economic and ecological advantages, that are responsible for this spectacular growth.

In the world market for fermentation products (ethanol excluded), which was estimated at US $14.1 billion for 2004 (and, with an average annual growth rate of 4.7%, can therefore be expected to reach US $17.8 billion in 2009), the amino acids are the second most important category, after antibiotics, with fermentation products exhibiting the highest growth rates (Maerz 2005) (Fig. 2).

Extraction of amino acids from protein hydrolysate as a method of obtaining L-amino acids is now of only limited importance; although still relevant for production of L-serine, L-proline, L-hydroxy-proline, and L-tyrosine, for example, it is not suitable for large-scale production of amino acids. The extraction method for obtaining L-glutamate was superseded nearly 50 years ago by fermentation, following a sharp increase in demand for the flavor-enhancer MSG. The discovery of the soil bacterium, *Corynebacterium glutamicum*, which is capable of producing L-glutamic acid with high productivity from sugar, paved the way for the success of the fermentation technique in amino acid production (Kinoshita et al. 1957). It was advantageous here that the wild strain could be used on an industrial scale under optimized fermentation conditions for mass production of glutamate. Glutamate biosynthesis and methods for improving production strains have been investigated in depth (Kimura 2003). The fermentation process is in principle very simple: a fermentation tank is charged under sterile conditions with a culture medium containing a suitable carbon source, such as sugar cane syrup, as well as the required nitrogen, sulfur, and phosphorus sources, and some trace elements. A culture of the production strain prepared in a prefermenter is added to the fermentation tank and stirred under specified conditions (temperature, pH, aeration). The L-glutamic acid released by the microorganism into the fermentation solution is then obtained by crystallization in the recovery section of the fermentation plant. MSG (1.5 million tons) is currently produced each year by this method, making L-glutamic acid the number one amino acid in terms of production capacity and demand (Ajinomoto 2003).

Advances in fermentation technology and strain improvement of amino acid producing microorganisms (Ikeda 2003) have enabled industrial-scale production of L-lysine as well as glutamate (de Graaf et al. 2001; Pfefferle et al. 2003). A contributory factor here is a deeper knowledge of the amino acid overproducer, *C. glutamicum*, the complete genomic sequence of which has since been determined (Kalinowski et al. 2003). The spectacular rise in demand for lysine, which as a limiting amino acid is a preferred additive to animal feeds for pig breeding (as the first limiting amino acid) and poultry (second limiting amino acid, after methionine), can be seen in Fig. 3. The demand for lysine

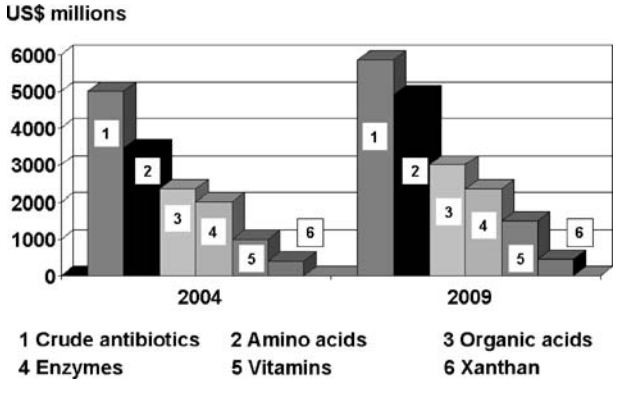

Fig. 2 Global market for fermentation products (Maerz, 2005). The largest fermentation product is ethanol (about US $12 billion). Global consumption of ethanol is expected to rise to 41.9 billion liters by 2006 (http://www.marketresearch.com/map/prod/876164.html. Cited 22 August 2005) Its growth is predicted to increase by 30% in 2009 as a methyl-*tert*-butyl ether replacement in the US

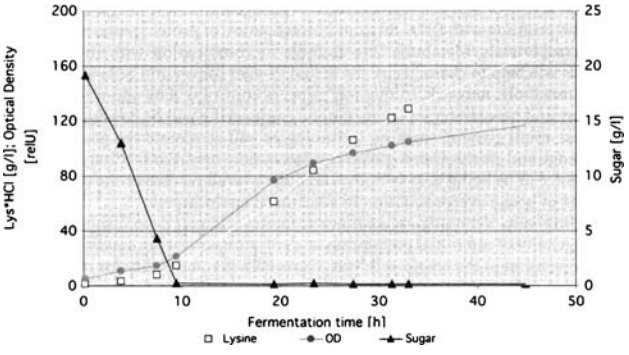

Fig. 4 Technical lysine fed-batch fermentation; sugar feeding is lower than the maximal sugar consumption rate resulting in a carbon limitation during the feed period (Pfefferle et al., 2003). The lysine fed-batch fermentation using overproducing strains of *C. glutamicum* is commercialized in the Biolys process

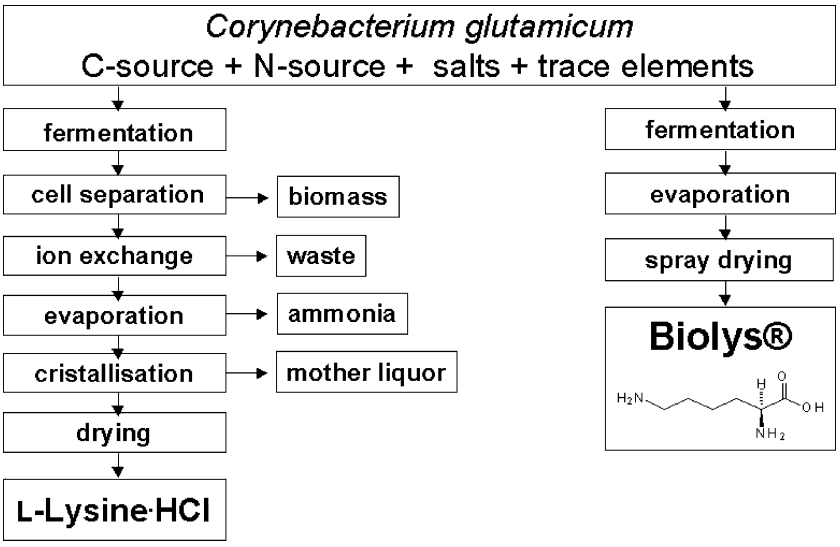

Fig. 5 Biolys production scheme (Patent EP 533039) compared to lysine hydrochloride production scheme

(calculated as lysine hydrochloride) in 2005 is estimated at 850,000 tons (Ajinomoto 2004). The main producers of lysine are the companies Ajinomoto (Japan), ADM (USA), Cheil-Jedang (South Korea), and Global BioChem (China) as well as BASF and Degussa (Germany). The strains used are exclusively high-performance mutants of *C. glutamicum*, usually fermented by the fed-batch process, in which nutrients are added in a controlled manner in accordance with the requirements of the culture solution, allowing optimal yields and productivities. Figure 4 shows a typical diagram for a fed-batch fermentation. Competitiveness is determined not only by the performance of the production strain, but can also be increased by a conveniently produced product form. Thus, in addition to the classic product form lysine hydrochloride, other forms such as granulated lysine sulfate (Biolys) and liquid lysine have also become established where the production is more economical and generates less liquid and solid waste. Figure 5 shows the process scheme for the Biolys production developed by Degussa (Binder et al. 1995), as compared with the lysine hydrochloride variant.

The fermentation method of production is also well established for the amino acids L-threonine (Debabov 2003) and L-tryptophan (Ikeda and Katsumata 1999), which are important as the second and third limiting amino acids in growing pigs. In this case, recombinant strains of *Escherichia coli* have proven to be particularly productive. World requirements for 2005 have been projected at 70,000 tons for L-threonine and 3,000 tons for L-tryptophan (Ajinomoto 2004).

The amino acids L-phenylalanine (Cordwell 1999) and L-cysteine (Wacker 2004), both of which were previously produced mainly with the help of enzymes, can now be obtained more cost effectively by fermentation with *E. coli* strains and are thus available to a larger and growing market. Almost all proteinogenic amino acids, with a few exceptions, can be produced industrially by specially developed mutants of *C. glutamicum* or *E. coli*. Table 1 shows the performance of these mutants.

One exception is the sulfur-containing amino acid methionine, which, as first limiting amino acid in poultry, is of particular importance. Methionine has been manufactured synthetically, i.e., as the racemate (DL-methionine), from the starting materials acrolein, hydrocyanic acid, methyl mercaptan, and ammonia, and marketed as a feed additive for more than 50 years. The fact that the D-form, not found in nature, is enzymatically converted into the nutritive L-form in the animal organism by means of an oxidase and

Table 1 Selected amino acid-producing strains (Ikeda 2003)

Amino acid	Strain/mutant	Titer (g/l)	Estimated yield (g/100 g sucrose)
L-Lysine HCl	*C. glutamicum* B-6	100	40–50
L-Threonine	*E. coli* KY 10935	100	40–50
L-Tryptophan	*C. glutamicum* KY9218/pIK9960	58	20–25
L-Tryptophan	*E. coli*	45	20–25
L-Phenylalanine	*E. coli* MWPWJ304/pMW16	51	20–25
L-Arginine	*Brevibacterium flavum* AJ12429	36	30–40
L-Histidine	*C. glutamicum* F81/pCH99	23	15–20
L-Isoleucine	*E. coli* H-8461	30	20–30
L-Serine	*Methylobacterium* sp. MN43	65	30–35
L-Valine	*C. glutamicum* VR 3	99	30–40

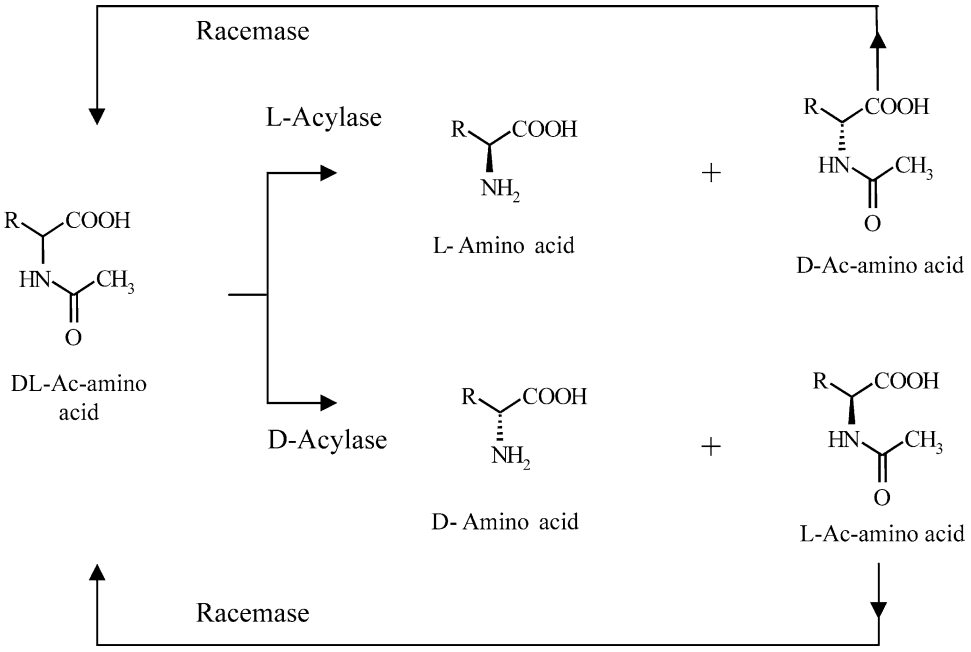

Fig. 6 L-Amino acid/D-amino acid production using acylases. Economically important targets: L-methionine, L-valine, D-valine, L-α-aminobutyric acid, D-phenylalanine, and analogs

transaminase allows direct use of the synthetic racemic mixture. For other amino acids such as lysine and threonine, there is no comparable enzyme system for conversion of the D-form, so that for these amino acids, it is necessary to produce the pure L-form. Despite the experience gained from lysine and threonine fermentation, attempts to develop a cost-effective production of L-methionine by the fermentation pathway have so far proved unsuccessful.

Enzymatic production of proteinogenic amino acids

Enzyme catalysis is now well established in the chemical industry (for production of fine chemicals, for example), and the potential of the method is far from being exhaustively explored (Drauz and Waldmann 2002). Industrial exploitation of enzymes for production of L-amino acids began almost 40 years ago in Japan with the resolution of

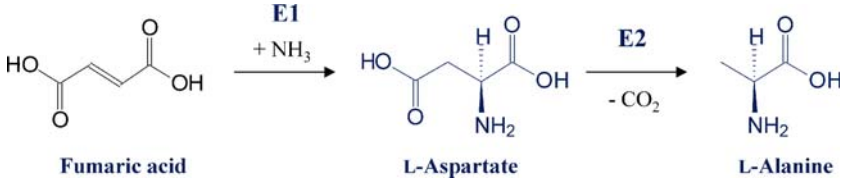

Fig. 7 Enzymatic production of L-aspartate and L-alanine based on fumaric acid E1 aspartate ammonia lyase (aspartase) from *E. coli*, E2 aspartate β-decarboxylase from *Pseudomonas dacunhae*

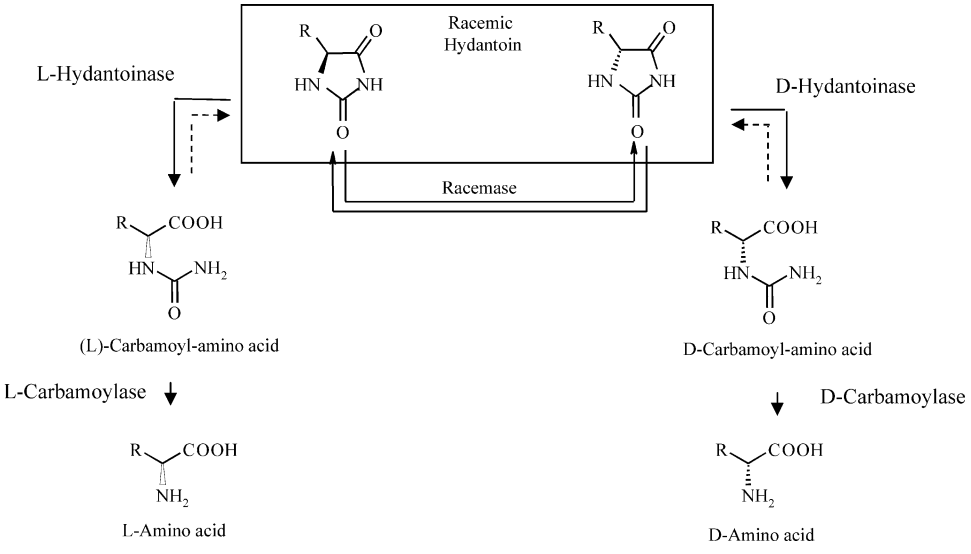

Fig. 8 D-Amino acid/L-amino acid production using hydantoinases/carbamoylases. Economically important targets: aromatic D-amino acids (D-phenylglycine, *p*-hydroxy-D-phenylglycine), D-serine, L-methionine, L-phosphinotricine

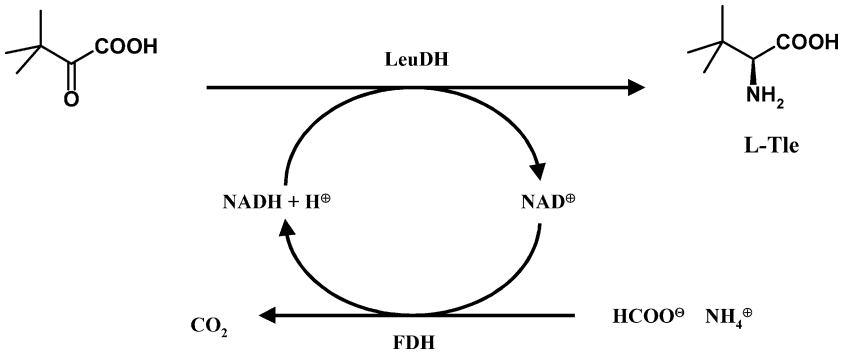

Fig. 9 Production of L-*tert*-leucine (*L-Tle*) from trimethyl pyruvate. Leucine dehydrogenase (*LeuDH*) catalyses reductive amination of ammonium trimethyl pyruvate; formate dehydrogenase (*FDH*) regenerates cofactor NAD^+ to NADH by oxidation of formate to carbon dioxide

N-acetyl DL-amino acids by immobilized acylase (Chibata 1978) (Fig. 6). For production of L-methionine, which is required for infusion solutions and special diets, this continues to be the method of choice, enzymatic resolution with acylase of *Aspergillus oryzae* in the enzyme membrane reactor (EMR) to minimize enzyme consumption having proved especially useful (Woeltinger et al. 2005). Several hundred tons of L-methionine and L-valine are now produced each year using EMR technology. A new enzymatic pathway for L-methionine has recently been proposed (Weckbecker and Hummel 2004). This consists of enzymatic conversion of DL-methionine by means of the enzymes D-amino acid oxidase and leucine dehydrogenase, both of which can be expressed in a recombinant *E. coli* host strain.

L-Aspartic acid is another amino acid that is preferably obtained enzymatically. Aspartase-catalyzed addition of ammonia to fumaric acid leads directly to L-aspartate, which is required in large quantities for the sweetener Aspartame. L-Aspartate is also a starting material for enzymatic production of L-alanine using immobilized aspartate β-decarboxylase (Fig. 7) (Calton 1992a,b).

For L-cysteine, which previously was produced mainly by electrochemical reduction of L-cystine obtained from protein hydrolysis, an industrially used enzymatic process exists in which the thiazoline derivative DL-2-amino-2-thiazoline-4-carboxylic acid (ATC) is converted with the help of three enzymes (L-ATC hydrolase, *S*-carbamoyl-L-cysteine hydrolase, and ATC racemase) from *Pseudomonas thiazolinophilum* (Pae et al. 1992). However, one may expect that modern methods of strain development will lead to the establishment of fermentation technology in L-cysteine production.

Enzymatic production of nonproteinogenic amino acids

Enzyme catalysis is a particularly elegant and popular method of producing D-amino acids and nonproteinogenic L-amino acids. D-Amino acids are obtained as a by-product of resolution in the production of L-amino acids. They can also be produced directly, e.g., with a D-specific acylase, from racemic acetyl amino acids (Fig. 6). The hydantoinase/carbamoylase system is also used industrially to produce D-phenylglycine and *p*-hydroxy-D-phenylglycine, which are building blocks for the semisynthetic antibiotics ampicillin and amoxycillin. It has recently become possible, using modern molecular biological methods (directed evolution), to

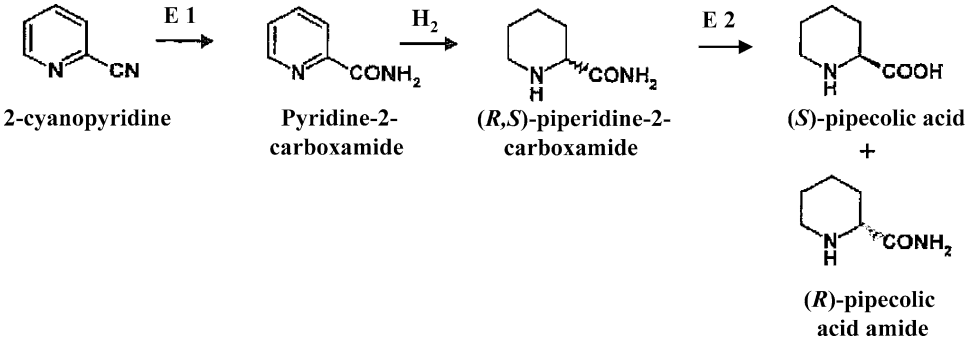

Fig. 10 Amidase-catalyzed production of (*S*)-pipecolic acid. E1, Nitrile hydratase (*Rhodococcus rhodochrous*); E2, (*S*)-specific amidase (*P. fluorescens*)

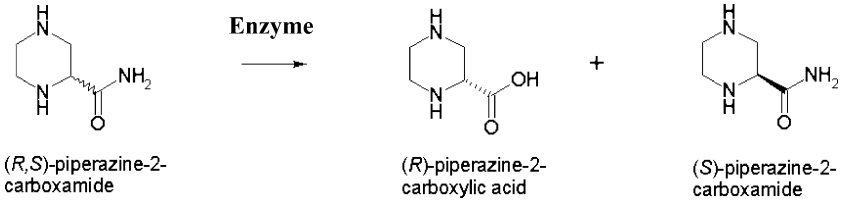

Fig. 11 Amidase-catalyzed production of (*R*)-piperazine-2-carboxylic acid (pipcarboxacid). Enzyme, (*R*)-specific amidase (coding gene isolated from *Burgholderia* sp. and cloned into *E. coli*)

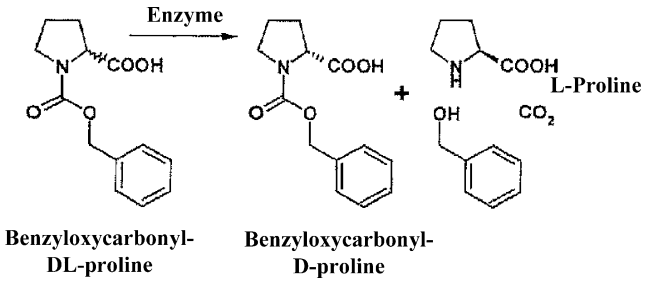

Fig. 12 Process for the production of benzyloxycarbonyl-D-proline. Enzyme, *N*-acyl-L-proline acylase from *Arthrobacter* sp

switch the D-specificity of hydantoinases to L-specificity (May et al. 2000). In addition, it became feasible to combine racemases with D- or L-selective hydantoinases and carbamoylases in highly efficient and tailor-made recombinant whole-cell systems, which can be used also to obtain a broad range of other D-amino acids as well as L-amino acids (May et al. 2002) (Fig. 8). The recently developed and optimized L- and D-hydantoinase systems accept a broad range of substrates and provide the optically pure amino acids in high yields.

Most industrially applied enzymatic processes use simple cofactor-independent enzyme systems such as hydrolases, lyases, and racemases. For production of L-*tert*-leucine, a synthetic building block in demand for novel pharmaceutical active ingredients as well as chiral auxiliaries and ligands, the simple methods have so far failed; it was possible to develop for this case a system in which reductive amination of ketoacids to L-amino acids with cofactor regeneration is successful even on an industrial scale. By using leucine dehydrogenase as the reducing enzyme, NADH as cofactor, and formate dehydrogenase as the regenerating enzyme, trimethyl pyruvate can be converted into L-*tert*-leucine (Fig. 9). The process and the development of particularly efficient enzymes (Slusarczyk et al. 2000) that allow large-scale production were recognized as especially innovative by the award of the German Future Prize 2002 (Degussa 2003).

Enzymatic production of amino acid derivatives

Chiral amino acid esters and amino acid amides can be obtained from racemic esters and amides by means of esterases, lipases, or amidases. An example for a commercially used (*S*)-specific amidase catalyzed reaction with whole cells of *Pseudomonas fluorescens* is the production

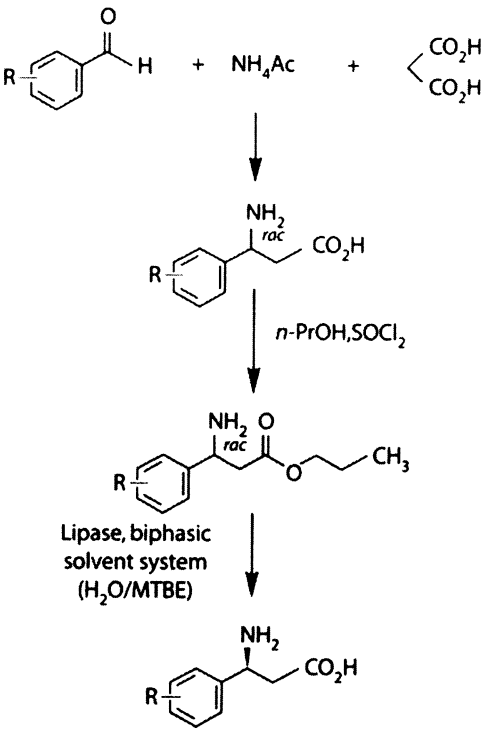

Fig. 14 Enzymatic resolution of β-amino acid esters with lipase yielding enantiomerically pure β-amino acids

of (*S*)-pipecolic acid and (*R*)-pipecolic acid amide from racemic (*R,S*)-pipecolic acid amide, which is synthesized in two steps from 2-cyanopyridine (Fig. 10). In a similar process, (*R,S*)-piperazine-2-carboxamide can be converted to (*R*)-piperazine-2-carboxamide and (*S*)-piperazine-2-carboxylic acid by means of the (*R*)-specific amidase from *Burgholderia* sp (Shaw et al. 2003). Cloning of the amidase-coding gene from the S2 organism *Burkholderia* sp. KIE153 into the S1 organism *E. coli* (pJKL7) has led to significant simplification of the synthetic pathway (Meyer et al. 2003) (Fig. 11).

A further example for an enzymatic production of a D-amino acid derivative is benzyloxycarbonyl-D-proline, which is used in the synthesis of Eletriptan, a drug for treatment of migraine (Ngo et al. 1997). Benzyloxycarbonyl-D-proline is obtained from the resolution of *N*-benzyloxycarbonyl-DL-proline by means of a proline selective acylase of *Arthrobacter* sp. (Fig. 12).

If provided with appropriate protective groups, amino acids can be linked enzymatically, e.g., with thermolysin

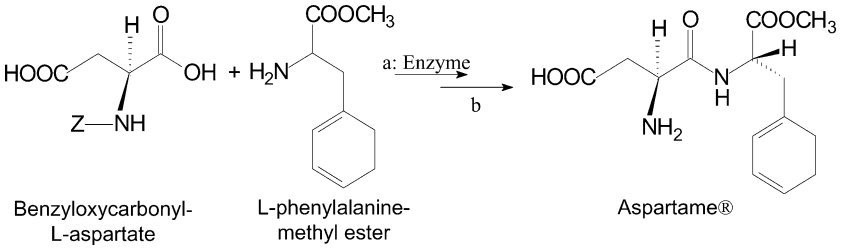

Fig. 13 Aspartame process. **a** peptide bonding catalyzed by thermolysine from *B. thermoproteolyticus*; **b** deprotecting the amino group

from *Bacillus thermoproteolyticus*, to give dipeptides (Eichhorn et al. 1997). A prominent example is the enzymatic synthesis of L-aspartyl-L-phenylalanine methyl ester (Fig. 13), which as the artificial low-calorie sweetener Aspartame, has succeeded in capturing an important market share in artificial sweeteners and is the preferred sweetener for drinks and sweet dishes. The global market volume for this peptide sweetener, with a sweetening power about 200 times that of sucrose, has been estimated at 14,000–15,000 tons in 2003 (Ajinomoto 2003).

Enantiomerically pure β-amino acids (Fig. 14) provide an example of a very new substance class that has become available on an industrial scale as a result of enzyme catalysis. Racemic β-phenylalanines, which are easily obtained by condensation of, for example, substituted benzaldehydes with malonic acid and ammonium acetate, are esterified with *n*-propanol, and the esters are cleaved with lipase in a biphasic solvent system to give the corresponding substituted enantiomerically pure β-phenylalanines (Groeger and Drauz 2003). β-Amino acids are attractive building blocks for a new generation of pharmaceutical active ingredients, which are currently undergoing clinical testing.

Outlook and prospects

Biotechnological production of amino acids today serves a market with strong prospects of growth. In the foreground are the fermentation processes, which are now widely established in the production of proteinogenic amino acids. The potential that will be leveraged in the future by modern methods and new findings in system biology will further stimulate and strengthen microbial amino acid production. (Wendisch et al. 2005).

Enzyme catalysis will remain the preferred production method for nonproteinogenic amino acids and amino acid derivatives. Modern methods such as directed evolution will allow development of customized, highly selective, and stable enzymes and whole cell biocatalysts, as well as efficient and ecologically sustainable production of the required products.

Both the fermentation and enzyme-based production methods play a central role in any discussion of the future of white biotechnology and could show the way to sustainable production of active ingredients, fine chemicals, and even certain bulk products (Sijbesma and Schepens 2004). It would be extremely interesting, for example, to assess the feasibility of implementing, in addition to the established chemical processes, a biorefinery concept based on renewable raw materials. “Green” biotechnology could also be used here to obtain products of interest from plants. As an example, transgenic plants with increased methionine (Aragao et al. 1999) and lysine content (Alvarez et al. 1998) have already been developed, but do not show commercial competitiveness at the present time.

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