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LECTURE TRANSCRIPT

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Development of a Commercial Process for (*S*)-β-Phenylalanine[1]

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ABSTRACT: The development of a commercial manufacturing route for (*S*)-β-phenylalanine **8**, a key pharmaceutical building block, is described. The different approaches which were investigated, based on catalytic asymmetric hydrogenation of enamide intermediates and on biocatalysis using acylase and lipase hydrolyses, are compared. The lipase resolution route was chosen for scale-up, and the final two-step process, based on readily available raw materials, is shown to be robust at full manufacturing scale

INTRODUCTION

The β-amino acid motif is becoming more common as a component of new pharmaceutical products, one of the reasons being the high stability of the β-amino acid peptide bond towards protease hydrolysis.[2] In addition, β-amino acid subunits are found in a variety of natural products. For example, the (*S*)-β-phenylalanine residue is found in pyloricidin A (**1**) and moiramide A (**2**).[3] In addition, the (*R*)-enantiomers of aromatic β-amino acids are present in cyclic peptides such as the astins, chondramides, and geodiamolides.[3] More recently, a number of pharmaceuticals containing a β-amino acid unit have been developed, such as otamixaban **3** (Sanofi-Aventis), and sitagliptin **5** (Merck), or where a β-amino acid is used as an intermediate, e.g. maraviroc **4** (Pfizer) (Figure 1).

The appearance of these products in development, together with a number of other target molecules containing an aromatic β-amino acid subunit, such as **6** and **7**,[4] was the starting point for our work on an enantioselective synthesis of this class of molecule, which could be implemented at a commercial scale. This lecture transcript summarises the work carried out at Evonik (previously Degussa), together with our academic collaborators, which led finally to a robust production process for (*S*)-3-amino-3-phenylpropanoic acid [(*S*)-β-phenylalanine] (**8**). A development process for the manufacture of **8** has been published as part of a synthesis of maraviroc,[5] but this involved a classical resolution step, and was not suitable for development to full manufacturing scale.

A variety of synthetic routes have been developed to prepare β-amino acids, and this type of structure has often been used to test the efficiency of new catalytic asymmetric syntheses.[3,6] A summary of selected routes to **8** is shown in Scheme 1. They can be divided up into classical chemical methods, such as the Arndt−Eistert chain extension,[7] diastereoselective processes, e.g. using a chiral amine base,[8] catalytic asymmetric hydrogenation reactions, and enzymatic methods. Our efforts focused on the latter two routes, and are discussed in more detail below.

CATALYTIC ASYMMETRIC HYDROGENATION APPROACHES

The asymmetric hydrogenation of 3-aminoacrylic acid derivatives differs from that of the isomeric 2-aminoacrylic acid derivatives, in that the starting material is formed as a mixture of *E*- and *Z*-enamides, which hydrogenate at different rates, and with different enantioselectivities. Our first work in this area was done in collaboration with Börner's group at Rostock, where we were able to show that high enantioselectivities were obtainable with *E*:*Z* mixtures of enamides, using a cationic Rh(I)-DuPHOS catalyst, simply by reducing the hydrogenation pressure from 30−40 to 1 bar (1 mol % catalyst loading, methanol, 25 °C).[9] These initial encouraging results led us to conduct further work with the Börner group on the design of a series of tunable bis-phospholane ligands, where the bite angle and the electron density of the ligand could be varied.[10] The first of these ligands, originally called MalPHOS (**9**), was later marketed as catASium M.[11] Hydrogenation of both the *E*- and *Z*-enamides using catalysts based on ligand **9** gave high enantioselectivity even with bulky substituents on the enamide, such as phenyl and isopropyl (1 mol % catalyst, methanol, 1 bar H_2, 25 °C). Further improvements in enantioselectivity were made using a series of diphosphine ligands based on camphor, where the phosphine groups could be tuned independently.[12] High enantioselectivity was obtained with both *E*- and *Z*-enamides, for example using the ligand **10** bearing both phenyl- and 3,5-xylyl-substituted phosphine groups (Scheme 2) (1 mol % catalyst, methanol or dichloromethane, 8 bar H_2, 25 °C).

At the same time, alternative asymmetric catalytic routes to **8** were examined. As β-keto-esters are readily available, their oximes were tested as substrates for asymmetric hydrogenation. A screening program was run, using ligands from a wide range of families, and high conversion and enantioselectivity were found using the ferrocenyl ligand Josiphos-PPF-P-tBu_2. Using 1 mol % of this ligand, and a hydrogen pressure of 20 bar, conversion to the hydroxylamine ether **11** was achieved in 91% yield and with 94% ee.[13] A second hydrogenation step, this time with a palladium/carbon catalyst, produced the β-phenylalanine ester **12** without any loss of enantioselectivity (Scheme 3).

In the last 10 years, many improvements have been made in ligand design, which have been instrumental in increasing the

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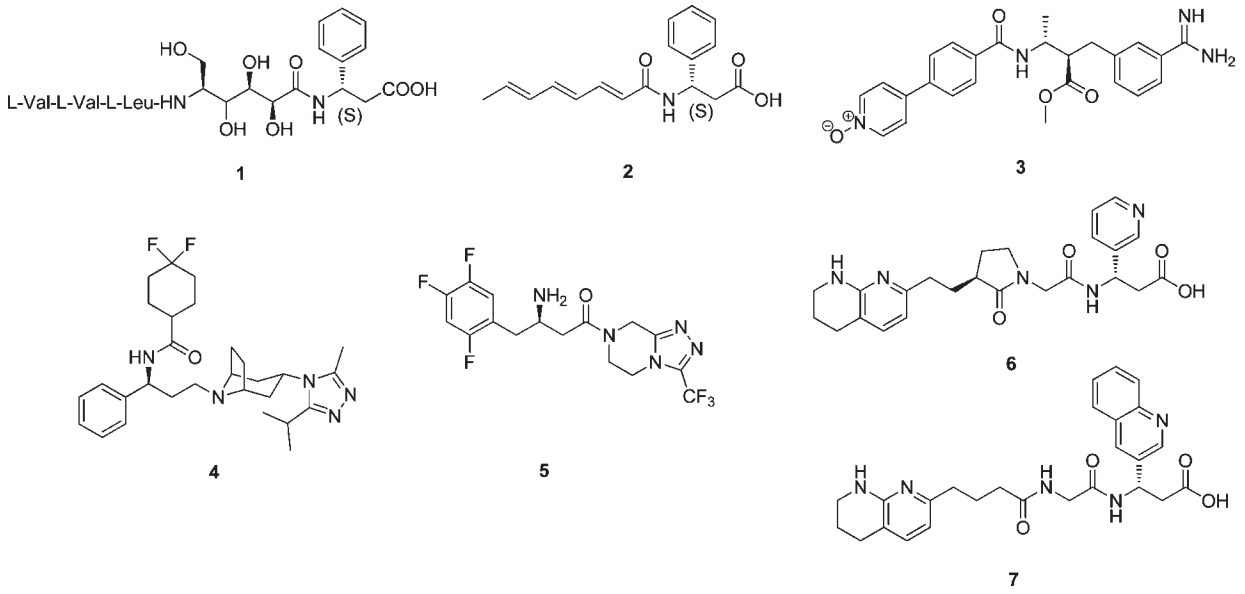
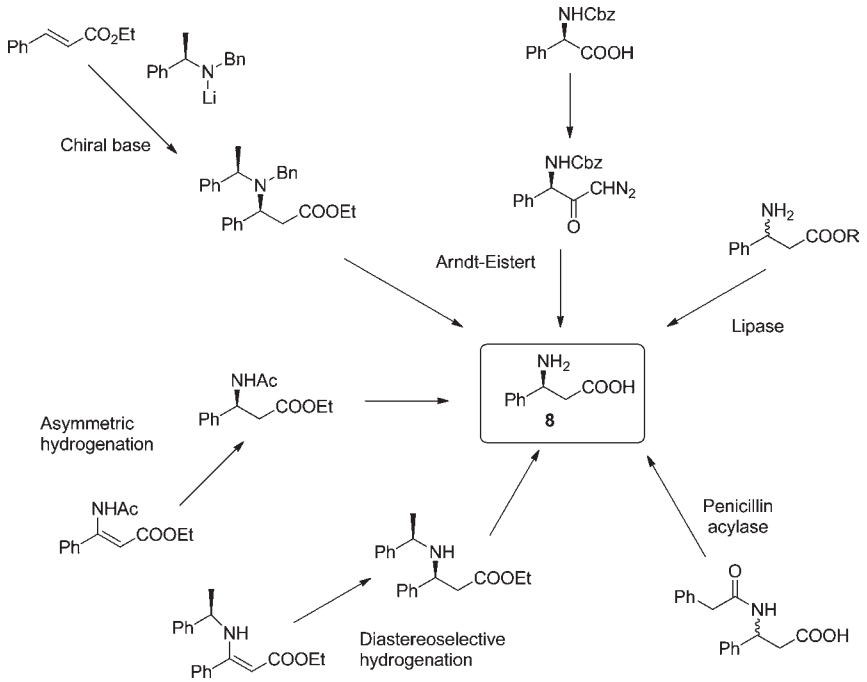


Figure 1. Natural products and pharmaceuticals based on β-amino acids.

Scheme 1. Summary of selected routes to (*S*)-β-phenylalanine



selectivity of catalytic asymmetric hydrogenation. A benchmark for the preparation of β-amino acid derivatives is set by the *P*-chiral ligands developed by the group of Xumu Zhang. This series of ligands, Tangphos, Duanphos, and Zhangphos, developed over a period of 8 years, can now deliver enantioselectivities of >95% on both the *E*- and *Z*-isomers of *N*-acyl enamides.[14] However, the long development time for a commercial catalytic asymmetric synthesis, together with the need to manufacture large quantities of a complex ligand for commercial manufacture of a β-amino acid, meant that we instigated a simultaneous development program for biocatalytic approaches to (*S*)-β-phenylalanine **8**.

BIOCATALYTIC APPROACHES

Although a large number of different enzymes and substrates have been used for the synthesis of β-amino acids,[15] practical routes to products such as **8** are based on readily accessible substrates and hydrolase enzymes. One of the earliest methods to be developed was the use of penicillin G acylase from *E. coli*,

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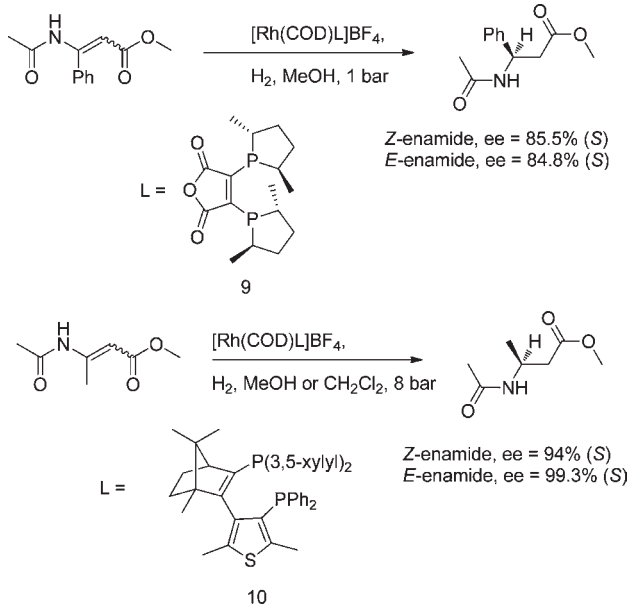
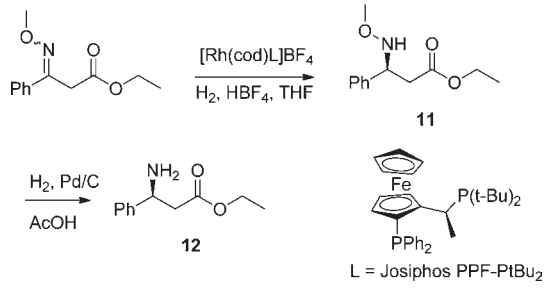
Scheme 2. Hydrogenation of enamides using tunable bis-phospholane ligands



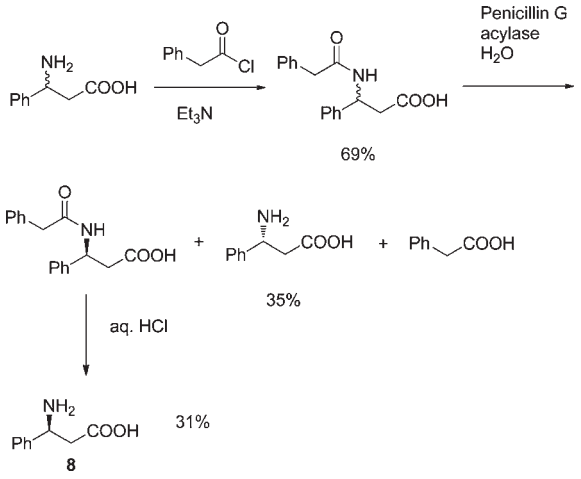
Scheme 3. β-Amino acids by reduction of oxime ethers



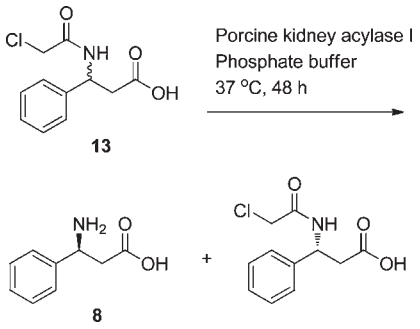
which was applied by Soloshonok et al. to the preparation of a range of aromatic β-amino acids.[16] The penicillin G acylase hydrolysis gives rise to the (*R*)-isomer of the β-amino acid: the (*S*)-isomer must be obtained by separation of the unreacted amide and subsequent chemical hydrolysis (Scheme 4). This, coupled with the high mass of the phenylacetyl protecting group and the need to separate the product from phenylacetic acid after the reaction, makes this process unsuitable for the manufacture of **8**.

Acylase enzymes were already tested for activity against *N*-acyl β-amino acids by Whitesides in 1989,[17] but contrary to the results found with α-amino acids, no activity was found with either porcine kidney acylase I or *Aspergillus* acylase. Despite this unpromising literature precedent, we screened a range of hydrolase enzymes against the *N*-acetyl and *N*-chloroacetyl derivatives of β-phenylalanine. We were pleased to find that porcine kidney acylase I had significant catalytic activity on the *N*-chloroacetyl β-amino acid **13**, although there was no activity on the corresponding *N*-acetyl β-amino acid.[18] On a preparative scale, a conversion of 49.5% was obtained after 48 h, with an enantioselectivity of >98%. Ion chromatography produced **8** in an isolated yield of 36% (Scheme 5).

Scheme 4. Hydrolysis using penicillin G acylase[16]



Scheme 5. Acylase route to aromatic β-amino acids



This route had the advantage of providing rapid access to a range of aromatic and heteroaromatic β-amino acids. However, it suffered from long reaction times, and the lack of a recombinant form of the porcine kidney acylase enzyme. Enzymes of animal origin are becoming less acceptable in the synthesis of pharmaceuticals, and in this case, no microbial alternative was available. We therefore turned our attention to the lipase route to **8**, where there was also a literature precedent. The enzymatic resolution of the ethyl ester has been achieved using the commercially available Amano PS lipase.[19] The enantioselectivity was given as 99% but was also stated to be very dependent on pH. When we repeated this work, we found that small changes in the operating procedure had major effects on the enantioselectivity of the isolated product. The pure acid **8** did indeed crystallise out with 99% ee at low concentrations, but the enantioselectivity in the bulk solution was only 85%. At higher concentrations, the (*R*)-enantiomer also crystallised from the reaction solution in variable amounts. We were pleased to find that changing from the ethyl ester to the propyl or butyl esters resulted in both a faster and a more enantioselective reaction (Table 1).[20]

The propyl ester **14** was chosen for further development. Further optimisation work demonstrated that the original purely aqueous reaction, with insoluble ester and acid phases, was not suitable for commercial operation. However, addition of sufficient acetone to bring the ester **14** into solution led to a marked reduction in the reaction rate. A two-phase system of *tert*-butyl

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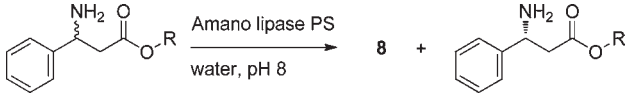
methyl ether and water, on the other hand, gave an operating system which had a number of advantages for scale-up (Figure 2). The racemic ester can be synthesised as a solution in MTBE and used directly without isolation. The (*R*)-ester remains in the organic phase and can be separated easily from the (*S*)-acid, which crystallises completely from the two-phase liquid mixture, and which has low solubility in MTBE. The lipase remains in the aqueous phase and can be separated from the product **8**, and recycled if required. The isolated (*S*)-*β*-Phenylalanine is of sufficient quality for downstream processing without any additional purification.

Together with the Landfester group at the University of Ulm, we investigated the possibility of performing the lipase hydrolysis in a mini-emulsion, instead of in a two-phase aqueous−organic system.[21] This allows for a more concentrated and homogeneous operation, or for a shorter reaction time or reduced enzyme charge (Table 2). The use of a surfactant and a hydrophobic additive allows the generation of nanodroplets with a defined size of 100−150 nm, using ultrasonic activation. Good conversion and isolated yields were found at reaction concentrations up to 605 g/L. However, there were some disadvantages to this process, which had to be resolved prior to scale-up. A substantial amount of acetone was required at the end of the reaction to break the emulsion, which negated the effect of the higher reaction concentration in terms of space-time yield. The reagents (hexadecane and lutensol) required to form the mini-emulsion have to be washed out completely from the isolated amino acid after filtration. In addition, the isolated yield was lower compared with that from biphasic conditions. As a result, the mini-emulsion method remains a laboratory process at present.

The scope of the lipase hydrolysis was studied with a range of aromatic and heteroaromatic propyl esters. Low activities were found with sterically hindered aromatics and with the furyl group (Table 3).[22] However, high enantioselectivities were found in all cases when the propyl ester of the racemic acid was used as substrate. Application of this hydrolysis to aliphatic substrates proved more difficult. The *β*-amino acid analogue of *tert*-leucine, β^3-neopentylglycine **15**, is a useful intermediate for pharmaceuticals requiring a *β*-amino acid with a bulky side chain. Enzyme screening showed that the best results were obtained with a *Candida Antarctica* lipase, but the ee was a moderate 40% (Scheme 6).[22] In this case, however, an alternative classical diastereomeric salt resolution gave ready access to this building block in high yield.[23]

Table 1. Effect of the alkyl group on the lipase hydrolysis to 8



R	conversion (%)	reaction time (h)	ee of (*S*)-acid (%)
CH_2-CH_3	37.8	6	85.1
$CH_2-CH_2-CH_3$	48.7	3	96.4
$CH_2-CH_2-CH_2-CH_3$	45.2	3	96.8

SCALE-UP OF THE LIPASE ROUTE TO (*S*)-*B*-PHENYLALANINE

The advantage of the lipase route to **8** is that there are only two isolated stages, the racemic *β*-amino acid **16** and the (*S*)-isomer **8**. Both stages produce crystalline products, which do not require any additional purification in normal operation (Scheme 7).

The first stage, the Rodionov reaction,[24] is a general single-step process to racemic aromatic *β*-amino acids. The yield of this reaction is around 50% at all process scales (kilo-lab, 3.3 kg of benzaldehyde, 45−52% yield; pilot plant, 40 kg of benzaldehyde, 47.5% yield; commercial plant, 340 kg of benzaldehyde, 50−52% yield). During our laboratory development work, we varied the reaction time and temperature, the reagent ratios, the rate of water quench, the agitation speed, and the cooling profile. None of the changes applied had a significant effect in improving the yield of **16** above the average of 50%. Pfizer workers reported sublimation of ammonium acetate on the condenser in their laboratory work, and changed to ammonium formate as the ammonia source for scale-up (yield 44%).[5] We encountered no problems with the use of ammonium acetate in the Rodionov

Table 2. Lipase hydrolysis in two-phase and mini-emulsion systems[21]

operating method	substrate (g/L)	reaction time (h)	conversion (%)	isolated yield (%)	ee (%)
two-phase	242	15	50	41	>99.4
mini-emulsion	242	8	49	38	>99.4
mini-emulsion	484	17	45	37	>99.4
mini-emulsion	605	24	42	35	>99.4

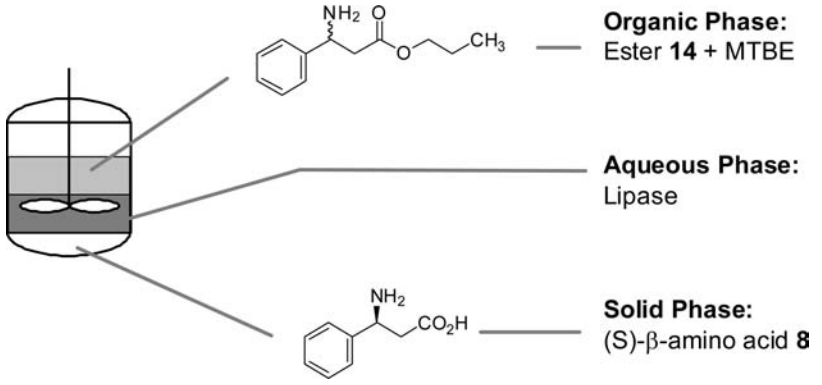
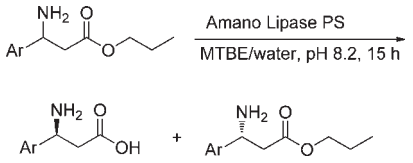


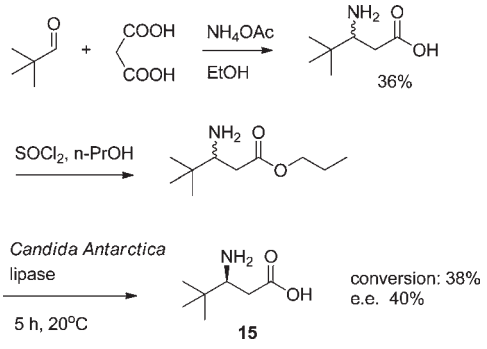
Figure 2. Schematic for the operation of the lipase hydrolysis.

Table 3. Scope of the lipase hydrolysis



aryl group	yield (*S*) − acid (%)	ee (*S*) − acid (%)
4-cyanophenyl	27	99
4-methylphenyl	50	98
4-bromophenyl	46	98
4-chlorophenyl	45	98
4-fluorophenyl	46	99
3-bromophenyl	34	>99
3-chlorophenyl	34	98
2-chlorophenyl	20	99
3,4-dichlorophenyl	34	99
2-furyl	16	99

Scheme 6. Lipase route to (*S*)-β^3-neopentylglycine

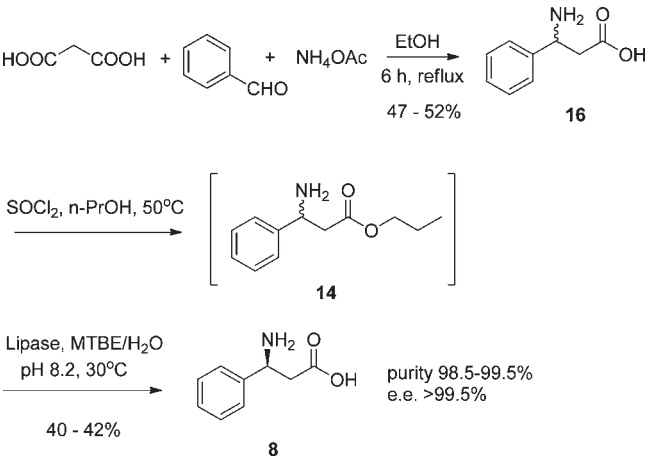


reaction at any of the scales operated. In their work on the mechanism of the Rodionov reaction, Tan and Weaver[25] described two possible mechanistic routes for the reaction and showed that the irreversible formation of cinnamic acid as a byproduct is a termination step in the process. The cinnamic acid is lost to the mother liquors and was not quantified by us.

The esterification stage operates very smoothly (1.1 equiv of thionyl chloride, *n*-propanol, 3 h, 50 °C), to give the racemic propyl ester **14**, which is not isolated. The excess *n*-propanol is removed by distillation, and the product is partitioned between water (at pH 3) and toluene. The aqueous layer is then adjusted to pH 8 and the free ester extracted into MTBE. This solution is mixed with an aqueous solution of the lipase (Amano lipase PS), and the two-phase mixture is stirred at 35 °C and at pH 8 until completion. The yield and quality of **8** was again unaffected by the reaction scale (kilo-lab, 3.7−7.4 kg of **16**, 38−41% yield; pilot plant, 100 kg of **16**, 43% yield; commercial plant, 430 kg of **16**, 42% yield). The reported yield of **8** is based on the racemic ester **14** charged and is relative to a maximum theoretical yield for the (*S*)-enantiomer of 50%. The chemical purity of the isolated (*S*)-β-phenylalanine was 98.5−99.5% in each case, and the optical purity >99.5% (usually the (*R*)-isomer was not detectable).

The organic layer containing the unreacted (*R*)-ester could be recovered and hydrolysed to give (*R*)-β-phenylalanine. Recovery

Scheme 7. Summary of the commercial route to (*S*)-β-phenylalanine



and recycle of the aqueous phase containing the lipase was also attempted, because the lipase is a major contributor towards the process cost. However, the lipase is partly inactivated during the 15-h reaction time, and gave only a 10−11% yield of **8** on recycle. However, a mixture of 75% recovered lipase solution, supplemented with a 50% charge of fresh lipase gave **8** in 41% isolated yield. The total enzyme charge of 125% of the original amount to a recycle batch takes account of the partial inactivation of the recycled lipase. It was possible to recycle the aqueous liquors 5 times in this way, giving yields of **8** in the range 41−43%, with <0.5% (*R*)-isomer by HPLC. The total lipase requirement per batch was thus 58% of a single-batch charge.

CONCLUSION

A number of laboratory routes to (*S*)-β-phenylalanine **8** have been developed. Of the metal-catalysed and biocatalytic routes studied, the lipase hydrolysis of the racemic propyl ester **14** was chosen for scale-up. This process is robust and has been operated at all scales from kilo-lab to full commercial plant. A rapid and efficient route to **8** and to other aromatic β-amino acids from simple starting materials has thus been achieved.

EXPERIMENTAL SECTION

All raw materials, reagents and solvents were purchased from commercial suppliers and used without further purification. All reactions were performed under an atmosphere of nitrogen. Lipase PS from *Burkholderia cepacia* was purchased from Amano, Japan.

Racemic 3-Amino-3-phenylpropanoic Acid: 16. Ethanol (2550 L) was charged to a 8000-L glass-lined reactor, together with ammonium acetate (617.5 kg, 8.01 kmol) and malonic acid (499.8 kg, 4.80 kmol). Benzaldehyde (340 kg, 3.20 kmol) was added, and the reaction mixture was heated to reflux (~80 °C). The reaction was held at 78−82 °C for 6 h, during which time carbon dioxide was evolved, and a clear solution was formed, followed by crystallisation of the amino acid. The reaction was cooled to 35−40 °C, and water (1530 L) was added over ~1 h. The suspension was further cooled to ~5 °C and centrifuged in portions, washing the crystals with water (total 350 L) and ethanol (total 350 L). The product was dried at 50 °C in vacuo to a residual solvent level of <0.3%, to give the dry amino acid

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16 (260 kg, 49.1%). Assay (HPLC area %) >98%, cinnamic acid <1.0%.

(*S*)-3-Amino-3-phenylpropanoic Acid: 8. The racemic amino acid **16** (430 kg, 2.60 kmol) and *n*-propanol (1935 L, 25.6 kmol) were charged to a 4000-L glass-lined reactor. Thionyl chloride (341 kg, 2.87 kmol) was added over 1−2 h, at a reaction temperature of <40 °C, while the off-gases (SO_2 and HCl) were absorbed in an NaOH scrubber. Following the addition, the reaction was held for 3 h at 47−50 °C for complete formation of the propyl ester. Unreacted thionyl chloride and *n*-propanol (∼1300 L) were removed by distillation (45 °C, 50 mbar), and then toluene (850 L) was added and the distillation repeated to ensure complete removal of *n*-propanol. Water (1500 L) was added, and the propyl ester was extracted into the aqueous phase. The aqueous layer was adjusted to pH 3−4 with 25% NaOH solution, and any residual organic solvent was removed by distillation (45 °C, 50 mbar). The cooled aqueous solution was stirred with *tert*-butyl methyl ether (MTBE) (600 L) and the pH adjusted to 8.0−8.2 with 25% NaOH (∼300 L). The layers were separated, and the aqueous layer was extracted with MTBE (600 L). Amano lipase PS (21 kg) was dissolved in water (800 L) and filtered into a 4000-L glass-lined reactor. The filter was washed with water (400 L). The MTBE extracts were added to the lipase solution and stirred for 15 h at 28−30 °C, while maintaining a pH of 8.1−8.3 by the addition of 25% NaOH. During this period, the *β*-amino acid **8** crystallised from the reaction. The product was centrifuged in portions and washed with acetone (total 2 × 200 L). The wet product was dried in vacuo to give the pure (*S*)-*β*-amino acid **8** (178 kg, 41.3%). Assay (titration) 99.0%, assay (HPLC, area %) 99.5%, (*R*)-enantiomer (chiral phase HPLC) <0.3%.

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