Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR),
OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
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OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.

Title: STEREOSELECTIVE PROCESS FOR THE SYNTHESIS OF (D)-2-AMINO-5-PHENYL-PENTANOIC OR ALKYL ESTER THEREOF

Abstract: The present invention provides a process for preparing a compound of formula (I); wherein R is a C₁⁻C₆ alkyl; or a salt thereof; comprising (c) hydrolyzing (D,L)-N-acyethyl-2-amino-5-phenylpentanoic acid with a suitable base in the presence of D-aminoacylase to provide (D)-2-amino-5-phenylpentanoic acid; and (d) esterifying (D)-2-amino-5-phenylpentanoic acid with an alkane. In a further embodiment, the present invention provides a process for selectively preparing (D)-2-amino-5-phenylpentanoic acid comprising hydrolyzing (D,L)-N-acyethyl-2-amino-5-phenyl pentanoic acid with a suitable base in the presence of D-aminoacylase. In a still further embodiment, the present invention provides an improved process for preparing a growth hormone secretagogue compound of formula (II) disclosed herein.
STEREOSELECTIVE PROCESS FOR THE SYNTHESIS OF (D)-2-AMINO-5-PHENYLPENTANOIC OR ALKYL ESTER THEREOF

BACKGROUND OF THE INVENTION

This invention relates to the field of pharmaceutical chemistry, and provides and advantageous process for preparing key intermediates in the production of compounds useful as growth hormone secretagogues.

(D)-2-amino-5-phenylpentanoic acid, ethyl ester is an intermediate to pharmaceutically active compounds (see, e.g., U.S. Patent No. 6,329,342 B1; as well as PCT International Publ. No. WO 99/08699, published Feb. 25, 1999, and PCT International Publ. No. WO 00/49037, published Aug. 24, 2000). According to the procedures described in the above-mentioned patent and patent applications, this intermediate is constructed by resolving the racemic mixture (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid via an enzymatic-catalyzed amide hydrolysis of isomer (A), removing it, then isolating the desired isomer (B) once the undesired isomer has been removed. The desired isomer is then esterified using ethanol to provide the ethyl ester intermediate.

\[
\begin{align*}
(A) & : \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2\text{COOH} \\
(B) & : \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2\text{COOH}
\end{align*}
\]

Acylase I (systematically N-acyl-L-amino-acid amidohydrolase) is the enzyme used to catalyze the amide hydrolysis step. This enzyme is very specific in that it hydrolyzes only N-acyl derivatives of neutral L-amino acids. In this particular reaction, this translates to the hydrolysis of the undesired isomer, isomer (A) to L-2-5-aminopentanoic acid, which subsequently solidifies and must be filtered. The remaining solution is then purified and the desired product is isolated.

Thus, there is a need for an improved process for the selective amide hydrolysis of (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid. Such a process would reduce the overall reaction time, the number of filtrations employed, the amount of reagents used, and eliminate a step in the overall synthesis.
BRIEF SUMMARY OF THE INVENTION

The present invention provides a process for preparing a compound of formula (I)

![Chemical structure](image)

(II)

wherein R is a C₁-C₆ alkyl; or a salt thereof;

comprising:

(a) hydrolyzing (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid with a suitable base in the presence of D-aminoacyclase to provide (D)-2-amino-5-phenylpentanoic acid; and

(b) esterifying (D)-2-amino-5-phenylpentanoic acid with an alkanol.

In a further embodiment, the present invention provides a process for selectively preparing (D)-2-amino-5-phenylpentanoic acid comprising hydrolyzing (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid with a suitable base in the presence of D-aminoacylase.

In a still further embodiment, the present invention provides an improved process for preparing a growth hormone secretagogue compound of formula (II) disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

General terms used in the description of chemical formulas bear their usual meanings. For example, the term "C₁-C₆ alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms. Typical C₁-C₆ alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, i-butyl, n-pentyl, isopentyl, n-hexyl, 2-methylpentyl, and the like. The term "C₁-C₄ alkyl" represents a straight or branched alkyl chain having from one to four carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, i-butyl, and t-butyl.

The term “alkanol” refers to an organic alcohol of from one to six carbons. Examples include methanol, ethanol, isopropanol, n-butanol, 1-pentanol, 2-pentanol, 1-hexanol, and the like.

The term “D-aminoacylase” refers to D-acyl-L-amino acid amidohydrolase. D-aminoacylase is an enzyme that catalyzes an amide hydrolysis of D-acyl derivatives of
neutral L-amino acids. D-aminoacylase is available commercially through Amano Enzyme Inc.

As used herein, the term “suitable base” refers to an alkali metal hydroxide or carbonate such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like. A preferred suitable base is potassium hydroxide.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the D-L system is also used in this document to denote absolute configuration, especially with reference to amino acids. In this system, a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix “D” is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon at the chiral center. The prefix “L” is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the left side of the carbon at the chiral center.

The designation “ ——— “ refers to a bond that protrudes forward out of the plane of the page.

The designation “ ——— “ refers to a bond that protrudes backward out of the plane of the page.

The designation “ ——— “ refers to a bond wherein the stereochemistry is not defined.

Many of the starting materials and compounds prepared by the process of this invention are further provided in U.S. Pat. No. 6,329,342 B1, this disclosure of which is

The process of the invention is illustrated in the Scheme below.

Scheme

\[
\begin{align*}
\text{(3)} & \quad \text{base} \quad \text{D-aminoacylase} \\
\text{(4a)} & \quad \text{(4b)} \\
\text{(R-OH)} & \\
\text{(I)} &
\end{align*}
\]

The instant process involves hydrolyzing the compound of formula (3) using a suitable base in the presence of D-aminoacylase (systematically N-acyl-D-amino acid amidohydrolase) to provide compounds (4a) and (4b). Compound (4a) is then esterified with an alkanol to provide a compound of formula (I).

As mentioned previously, suitable bases include alkali metal hydroxide or carbonate such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like. A preferred suitable base for the hydrolysis step is potassium hydroxide.
Solvents including solvent mixtures employed in the practice of this invention may affect the overall reaction, including reaction products and overall yield. It is necessary for this reaction to take place in an aqueous solvent, with water being most preferred. For example, water acts as reactant in the general reaction for enzymatic hydrolysis using D-aminoacylase (e.g. N-acyl-D-amino acid + H₂O <-> an acid + D-amino acid). Zinc²⁺ (preferably in the form of ZnCl) is used as a cofactor (or coenzyme or noncompetitive inhibitor) in this reaction. It activates D-aminoacylase so that it may bind to the substrate and the reaction may proceed. Data from Amano Enzyme, Inc. states that Cu²⁺ and Fe²⁺ may also act as inhibitors.

The hydrolysis reaction in the first step is conducted at temperatures ranging from about 20°C to about 150°C, preferably from about 30°C to about 80°C, most preferably from about 35°C to about 50°C. The hydrolysis reaction is maintained at a pH of from about 6.0 to 10.0, preferably from about 7.5 to about 8.5, more preferably from about 7.8 to about 8.2, most preferably at a pH of about 8.0. The pH may be adjusted using a suitable acid, most preferably concentrated hydrochloric acid.

As presently practiced, the hydrolysis reaction is carried out for a period of time ranging from about 1 to about 12 hours, preferably from about 4 to about 6 hours. The product of formula (4a) is then isolated and purified by techniques well known in the art, such as extraction, evaporation, filtration, trituration, chromatography, and recrystallization. Most preferably, the product of formula (4a) is isolated by filtration and washed with a suitable organic solvent such as heptane.

In the esterification step, the compound of formula (4a) is contacted with an alkanol. The selection of the suitable alkanol depends on the alkyl ester of formula (1) desired as end product. Most preferably, ethanol is used. The reaction is typically conducted in the presence of a suitable acid, such as concentrated hydrochloric acid.

The esterification reaction is conducted at temperatures ranging from about 50°C to about 100°C, preferably from about 70°C to about 90°C, most preferably from about 80°C to about 85°C.

The esterification step is carried out for a period of time ranging from about 2 to about 6 hours, preferably from about 3 to about 4 hours, most preferably to about 3 hours. Completion of the reaction is monitored by use of HPLC. A compound of
formula (I) is then isolated and purified by techniques well known in the art, such as extraction, evaporation, filtration, trituration, chromatography, and recrystallization.

In another embodiment, the present invention provides an improved process for preparing a compound of formula (II)

$$\text{(II)}$$

wherein:

R$^1$ is fluoro, chloro, bromo, -CF$_3$, C$_1$-C$_6$ alkoxy, or phenyl;

R$^2$ is −H or −CH$_3$;

R$^3$ and R$^4$ are each independently C$_1$-C$_6$ alkyl, or combine to form, with the nitrogen atom to which they are attached, pyrrolidinyl or 4-methylpiperidinyl; or a pharmaceutically acceptable salt thereof; the improvement comprising hydrolyzing (D,L)-N-acetyl-2-amino-5-phenylpentanoic acid with a suitable base in the presence of D-aminocyclase.

The improvement described immediately above involves the selective hydrolysis of the compound of formula (3) to provide the compound of formula (4a) and subsequently esterifying the compound of formula (4a) to provide a compound of formula (I). The desired compound of formula (II) may be prepared from a compound of formula (II) according to the procedures set forth in U.S. Pat. No. 6,329,342 B1, hereby incorporated by reference as if fully set forth.
For example, the compound of formula (I) is coupled with N-t-BOC–alpha-aminobutyric acid, de-esterified, and coupled with an intermediate of formula (5).

The BOC protective group is removed and the free base is isolated from the salt to provide the compound of formula (II).

The compounds of formula (II) may be administered in the form of acid addition salts. "The term "pharmaceutically acceptable salts thereof" refers to either an acid addition salt or a basic addition salt.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by formula (II). Illustrative inorganic acids that form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-phenoxy-benzoic, p-toluenesulphonic acid, and sulfonic acids such as benzenesulphonic acid, methanesulphonic acid, and 2-hydroxyethanesulphonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

The compounds of formula (II) are useful as growth hormone secretagogues. The compounds of formula (II) are further useful in the treatment of frailty, decreased bone mineral density, impaired exercise capacity, excessive adiposity and cardiovascular disease, particularly treatment of congestive heart failure and myocardial dysfunction.
In this document, all temperatures are stated in degrees Celsius. All amounts, ratios, concentrations, proportions and the like will be stated in weight units, unless otherwise stated, except for ratios of solvents, which are in volume units. As used in the examples the following terms have the indicated meanings; "ng" refers to nanograms; "µg" refers to micrograms; "mg" refers to milligrams; "g" refers to grams; "kg" refers to kilograms; "nmol" refers to nanomoles; "mmol" refers to millimoles; "mol" refers to moles; "µL" refers to microliters; "mL" refers to milliliters; "L" refers to liters; "°C." refers to degrees Celsius; "bp" refers to boiling point; "mm of Hg" refers to pressure in millimeters of mercury; "mp" refers to melting point; "nM" refers to nanomolar; "µM" refers to micromolar; "mM" refers to millimolar; "M" refers to molar; "HPLC" refers to high performance liquid chromatography; "HRMS" refers to high resolution mass spectrum.

**EXAMPLE 1**

![Chemical Structure](image)

A solution of 21% sodium ethoxide in ethanol (410 g, 1.266 mol) was added to a solution of diethylacetamidomalonate (250 g, 1.151 mol) dissolved in ethanol (915 mL). The reaction mixture was stirred for 2 hours at ambient temperature. 1-bromo-3-phenylpropane (229.1 grams, 1.151 mol) was then added over 15 minutes and the reaction mixture was stirred at 73 °C until complete as determined by HPLC (28 hours). The reaction mixture was solvent exchanged to ethyl acetate (1500 mL) and washed with water (1500 mL). The water layer was extracted with ethyl acetate (1 x 750 mL). The combined layers were washed with saturated sodium chloride solution (1 x 750 mL). The ethyl acetate solution was solvent exchanged to heptane and diluted to give a slurry volume of 3000 mL. The solids were filtered and washed with heptane (625 mL) to give 313 grams of 451840 at 95% purity (775) as a tan solid. ¹H nmr (CDCl₃): δ 1.18-1.23 (t,
6H), 1.37-1.50 (m, 2H), 2.02 (s, 3H), 2.34-2.41 (m, 2H), 2.58 – 2.62 (t6, 2H), 4.16-4.24 (q,4H), 6.76 (s, broad, 1H), 7.11-7.28 (m, 5H).

EXAMPLE 2

![Chemical Structure](image)

A slurry consisting of product of Example 1 (249.15 grams, 0.7428 mol) and 2.5 N sodium hydroxide solution was then heated at 100 °C for three hours. The reaction mixture was cooled to 30°C and the pH adjusted to 5.0 using concentrated hydrochloric acid. The solution was then heated to 100°C and the pH was held at 5.0 using concentrated hydrochloric acid as needed until the reaction was complete as determined by HPLC. The solution was filtered while hot through diatomaceous earth. The filtrate was cooled to 5-10°C and the pH adjusted to 1.0 using concentrated hydrochloric acid. The resulting slurry was stirred for 1 hour at 5°C, filtered, and dried in vacuum at 50°C to give 160.34 grams (92%) of the title compound as an off-white powder. \(^1\)H nmr (DMSO-d _6_): δ 1.60-1.71 (m, 4H), 1.86 (s, 3H), 2.56-2.59 (m, 2H), 2.19 – 4.23 (m, 1H), 7.16-7.30 (m, 5H), 8.14 (d, 1H).

EXAMPLE 3

![Chemical Structure](image)

A solution consisting of (DL)-N-acetyl-2-amino-5-phenylpentanoic acid (10.0 grams, 0.043 moles), zinc chloride (0.003 grams), 2 N potassium hydroxide solution (21.5 mL, 0.043 moles), and water (128.5 mL) was adjusted to a pH of 8.0 by the addition concentrated hydrochloric acid. To the reaction mixture was added D-aminoacylase (N-Acyl-D-amino acid amidohydrolase, 0.1 grams) which was then vigorously stirred for 12 hours at 40 °C while maintaining a pH of 8.0 by the addition of 2N potassium hydroxide.
and concentrated hydrochloric acid. The product was isolated by filtration, washed with heptane (20 mL) and dried in vacuum at 50 °C to give 3.89 grams (47.29%) of the above-identified product, (D)-N-amino-5-phenylpentanoic acid: 1H nmr (TFA-D):  δ 1.906-1.942 (m, 2H), 2.134-2.192 (m, 2H), 2.74-2.786 (m, 2H), 4.352-4.373 (m, 1H), 7.161-7.320 (m, 5H), 11.601(s, 6H).

EXAMPLE 4

Reflux was resumed the next morning for ~1 hour and then 50 mLs of ethyl acetate was added to the vessel. The solution was then concentrated down to ~30 mLs via atmospheric distillation. This sequence (i.e. addition of ethyl acetate followed by atmospheric concentration) was repeated twice more before a final addition of 30 mL of ethyl acetate to the warm mixture. The solution was cooled slowly to room temperature (over several hours) and the resulting slurry was stirred at room temperature for 40 minutes. Subsequent filtration and rinsing (once with 10 mLs of cold ethyl acetate), followed by vacuum drying at 50°C, yielded 2.47 grams (~92%) of the title compound. 1H nmr (DMSO-d6):  δ 1.15-1.21 (t, 3H), 1.50-1.89 (m, 4H), 2.48-2.67 (m, 2H), 3.92-3.98 (t, 1H), 4.08-4.25 (m, 2H), 7.12-7.29 (m, 5H), 8.76 (s, broad, 3H).

EXAMPLE 5

1.10 eq BOC-AIB, 1.05 eq CDMT, and 2.07 eq N-methylmorpholine are added to 11 volumes MTBE and the resulting slurry is stirred at room temperature 3-6 hours or until CDMT is less than 1% by HPLC. 1.00 eq of a compound of Example 4 is then added and the mixture is brought to reflux (55° C). The mixture is stirred at reflux 1-2
hours or until the compound of Example 4 is less than 1% by HPLC. It is then cooled to room temperature. 10 volumes 20% citric acid are added and the mixture is stirred 20-30 minutes until all solids are dissolved. The layers are allowed to settle 30 minutes and then the lower aqueous layer is separated from the organic layer. 10 volumes 5% sodium bicarbonate are then added to the organic phase and the mixture is stirred for 5-10 minutes. After settling for 30 minutes, the lower aqueous layer is again separated from the organic layer. 5 volumes DI water are then added to the organic phase. The mixture is heated to 40°C and stirred 5-10 minutes. After settling 30 minutes, the lower aqueous layer and the rag layer are separated from the organic layer. All aqueous layers are combined and neutralized with 50% caustic and then are disposed.

The organic phase is solvent exchanged from MTBE into heptane by atmospheric distillation at 6-7 volumes until the liquid temperature reaches 98°C. The distillate is then disposed. After cooling to 90°C, additional heptane is added to bring the level up to 10 volumes. The solution is cooled over 4 ½ hours to 0-5°C, with the product crystallizing from the mixture around 70-75°C. The slurry is filtered and the product cake is washed with 2-3 cake volumes cold heptane. The filtrate is then disposed. The product is dried under vacuum at 45°C.

$^1$H nmr (CDCl$_3$): δ 1.25-1.28 (t, 3H), 1.43 (s, 9H), 1.48 (s, 3H), 1.50 (s, 3H), 1.70-1.73 (m, 3H), 1.87-1.93 (m, 1H), 2.62-2.67 (m, 2H), 4.16-4.21 (m, 2H), 4.57-4.62 (m, 1H), 4.95 (s, 1H), 6.96 (s, broad, 1H), 7.16-7.19 (m, 3H), 7.26-7.33 (m, 2H).

EXAMPLE 6

A solution of the compound of Example 5 (40.0 grams, 0.0984 mol) and tetrahydrofuran was cooled to 5°C. A solution consisting of lithium hydroxide monohydrate (7.2 grams, 0.172 mol) and water (184 mL) was added to the reaction dropwise over 10 minutes while maintaining a temperature of 5-10°C. The reaction
stirred at 0-10°C until complete as determined by HPLC (2 hours). The pH of the reaction mixture was then adjusted to 2.0 using 6 N hydrochloric acid solution while maintaining 5-10°C. The product was extracted from the solution with ethyl acetate (1x 150 mL, 2 x 90 mL). The ethyl acetate extracts were combined, washed with saturated sodium chloride (1 x 120 mL), and dried using sodium sulfate (30 min). The ethyl acetate solution was solvent exchanged to heptane to crystallize. The solids were filtered and washed with heptane (120 mL), then dried under vacuum at 40 °C to give a white solid. (98%).

$^1$H nmr (DMSO-d$_6$): $\delta$ 1.32-1.37 (m, 15H), 1.57-1.75 (m, 4H), 2.51-2.58 (m, 2H), 4.23-4.27 (m, 1H), 6.85 (s, broad, 1H), 7.15-7.28 (m, 5H), 7.42 (d, 1H), 12.5 (s, broad, 1H).

The improved process of this invention allows for the elimination of one process step and the substantial reduction in the reaction of two steps. For example, according to the current process, the undesired enantiomer, (L)-N-acetyl-2-amino-5-phenylpentanoic acid stays in solution, thereby eliminating a separation step. The average reaction time for two additional steps is reduced by over twenty hours, while the amount of solvents needed is drastically reduced.
I CLAIM:

1. A process for preparing a compound of formula (I)

\[
\begin{array}{c}
\text{NH}_2 \\
\text{CO}_2\text{R}
\end{array}
\]

wherein R is a C₁-C₆ alkyl; or a salt thereof; comprising:

(a) hydrolyzing (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid with a suitable base in the presence of D-aminoacylase to provide (D)-2-amino-5-phenylpentanoic acid; and

(b) esterifying (D)-2-amino-5-phenylpentanoic acid with an alkanol.

2. A process according to Claim 1 wherein said alkanol is ethanol.

3. A process according to either of Claims 1 or 2 further comprising conducting step (a) at a temperature ranging from about 20°C to about 150°C.

4. A process according to Claim 3 wherein said temperature ranges from about 30°C to about 80°C.

5. A process according to Claim 3 wherein said temperature ranges from about 35°C to about 50°C.

6. A process according to any of Claims 1 through 5 further comprising conducting step (a) at a pH ranging from about 6.0 to about 10.0.

7. A process according to Claim 6 wherein said pH ranges from about 7.5 to about 8.5.
8. A process according to Claim 6 wherein said pH ranges from about 7.8 to about 8.2.

9. A process according to Claim 6 wherein said pH is about 8.0.

10. In a process for preparing a compound of formula (II)

![Chemical Structure](image)

wherein:

- $R^1$ is fluoro, chloro, bromo, -CF$_3$, C$_1$-C$_6$ alkoxy, or phenyl;
- $R^2$ is –H or –CH$_3$;
- $R^3$ and $R^4$ are each independently C$_1$-C$_6$ alkyl, or combine to form, with the nitrogen atom to which they are attached, pyrrolidinyl or 4-methylpiperidinyl; or a pharmaceutically acceptable salt thereof; the improvement comprising hydrolyzing (D,L)-N-acetyl-2-amino-5-phenylpentanoic acid with a suitable base in the presence of D-aminoacylase.

11. A process according to Claims 10 further comprising conducting step (a) at a temperature ranging from about 20°C to about 150°C.

12. A process according to Claim 11 wherein said temperature ranges from about 30°C to about 80°C.

13. A process according to Claim 11 wherein said temperature ranges from about 35°C to about 50°C.
14. A process according to any of Claims 10 through 13 further comprising conducting step (a) at a pH ranging from about 6.0 to about 10.0.

15. A process according to Claim 14 wherein said pH ranges from about 7.5 to about 8.5.

16. A process according to Claim 14 wherein said pH ranges from about 7.8 to about 8.2.

17. A process according to Claim 14 wherein said pH is about 8.0.

18. A process for selectively preparing (D)-2-amino-5-phenylpentanoic acid comprising hydrolyzing (D,L)-N-acetyl-2-amino-5-phenyl pentanoic acid with a suitable base in the presence of D-aminoacylase.

19. A process according to Claim 18 further comprising maintaining a temperature range of from about 20°C to about 150°C.

20. A process according to Claim 19 wherein said temperature ranges from about 30°C to about 80°C.

21. A process according to Claim 19 wherein said temperature ranges from about 35°C to about 50°C.

22. A process according to any of Claims 18 through 21 further comprising conducting step (a) at a pH ranging from about 6.0 to about 10.0.

23. A process according to Claim 22 wherein said pH ranges from about 7.5 to about 8.5.

24. A process according to Claim 22 wherein said pH ranges from about 7.8 to about 8.2.
25. A process according to Claim 22 wherein said pH is about 8.0.
## INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC 7 | C07C227/32 | C07C229/36 | C07D233/80 |

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| IPC 7 | C07C | C07D |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>US 6 329 342 B1 (KAUFFMAN RAYMOND F ET AL.) 11 December 2001 (2001-12-11) cited in the application column 65-69, paragraphs 1E,1F,1G,1H,1I,PREP.3 prep.10-12 and prep.13-14 column 76-79; examples 7,8,10 prep.17-18 column 81-83</td>
<td>1-25</td>
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**Further documents are listed in the continuation of box C.**

**Patient family members are listed in annex.**

- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another document or other special reason (as specified)
- **O** document referring to an oral disclosure, use, exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

**Special categories of cited documents**

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- **"X"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **"Y"** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **"A"** document member of the same patent family

**Date of the actual completion of the international search**

9 July 2003

**Date of mailing of the international search report**

21/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2 NL, 2280 HV Rijswijk Tel. (31-70) 940-2040, Tx 31 651 epo nl, Fax (31-70) 940-3016

Authorized officer

Seelmann, M
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>CHENAULT H K ET AL: &quot;KINETIC RESOLUTION OF UNNATURAL AND RARELY OCCURRING AMINO ACIDS: ENANTIOSELECTIVE HYDROLYSIS OF N-ACYL AMINO ACIDS CATALYZED BY ACYLASE I&quot; JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 111, no. 16, 2 August 1989 (1989-08-02), pages 6354-6364, XP0000940668 ISSN: 0002-7863 page 6354, left-hand column page 6355; table I page 6358; figure V page 6361, right-hand column, paragraphs 2-6 page 6362, left-hand column, paragraphs 2,3; table IV</td>
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