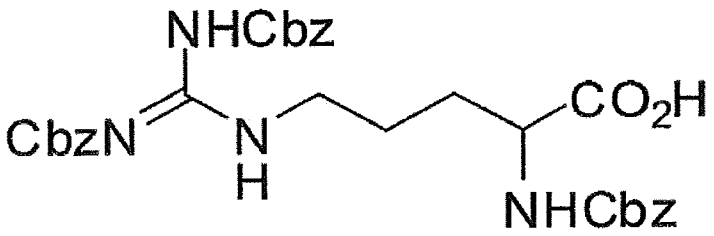
[0009]

Further, the present invention relates to a method for producing a tri-carbobenzoxy-arginine amine salt as a solid, comprising

adding an amine to a tri-carbobenzoxy-arginine represented by the following formula (2):

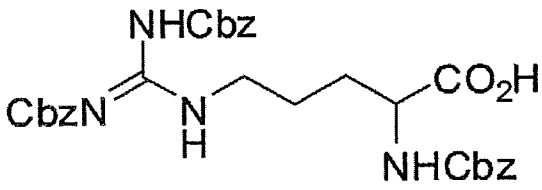
[Chemical Formula 4]



(2)

to obtain the tri-carbobenzoxy-arginine amine salt represented by the following formula (3):

[Chemical Formula 5]



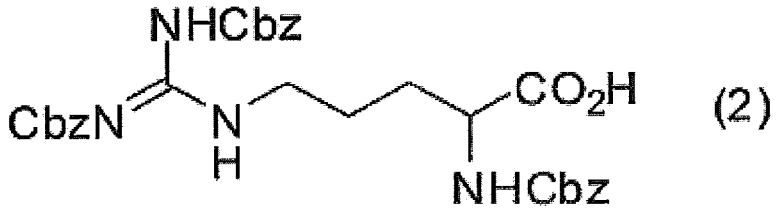
$NR^2R^3R^4$ (3)

wherein R^2, R^3 and R^4 represent the same groups as the above..

[0010]

Further, the present invention relates to a method for producing a tri-carbobenzoxy-arginine amine with high purity, comprising adding an acid to the obtained tri-carbobenzoxy-arginine amine salt to extract a tri-carbobenzoxy-arginine in an organic layer.

[0010a] In an aspect, there is provided a method for producing a tri-carbobenzoxy-arginine of the formula (2):



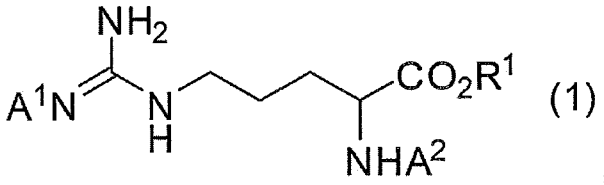
(2)

,

wherein Cbz represents a benzyloxycarbonyl group,

the method comprising:

adding carbobenzoxy chloride and a base in the presence of a surfactant to an arginine or arginine derivative of the formula (1) or a salt thereof:



(1)

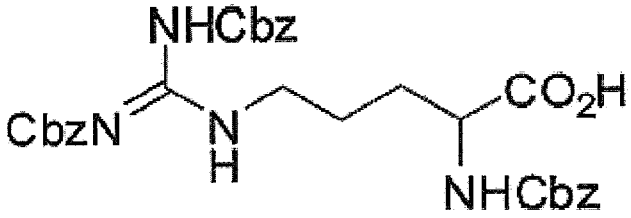
,

wherein A^1 and A^2 each represents an amino group protecting group or a hydrogen atom, and R^1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent, such that the arginine or arginine derivative of the formula (1) or a salt thereof is carbobenzoxylated,

wherein, in the adding, the carbobenzoxy chloride and the base are added to the arginine or arginine derivative of the formula (1) or a salt thereof in a bilayer system comprising water and an organic solvent, and

wherein the surfactant is selected from the group consisting of a carboxylic acid-type surfactant, a sulfonic acid-type surfactant, a sulfuric acid ester-type surfactant, a phosphoric acid ester-type surfactant and a quaternary ammonium salt-type surfactant.

[0010b] In another aspect, there is provided a method for producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a solid form,



$NR^2R^3R^4$ (3),

wherein R^2, R^3 and R^4 each represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

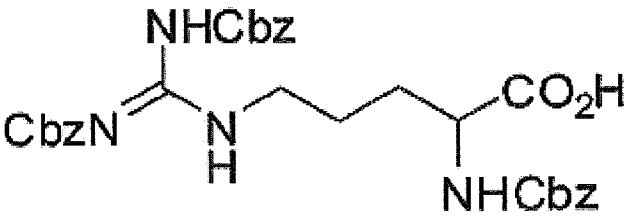
the method comprising:

producing a tri-carbobenzoxy-arginine by the method as described herein; and

adding an amine to a solution comprising the tri-carbobenzoxy-arginine such that the tri-carbobenzoxy-arginine amine salt in a solid form is obtained.

[0010c] In another aspect, there is provided a method for producing a tri-carbobenzoxy-arginine, comprising:

producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a solid form



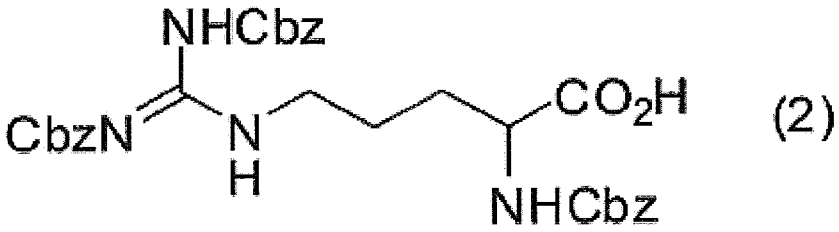
$NR^2R^3R^4$ (3),

wherein R^2, R^3 and R^4 each represents a hydrogen atom, an alkyl group

having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

by the following method comprising:

adding an amine to a tri-carbobenzoxy-arginine of the formula (2):



(2)

such that the tri-carbobenzoxy-arginine amine salt is obtained, and

isolating the obtained tri-carbobenzoxy-arginine amine salt,

and

adding an acid to the tri-carbobenzoxy-arginine amine salt to extract a tri-carbobenzoxy-arginine in an organic layer.

[0010d] In another aspect, there is provided a method for producing a tri-carbobenzoxy-arginine, comprising:

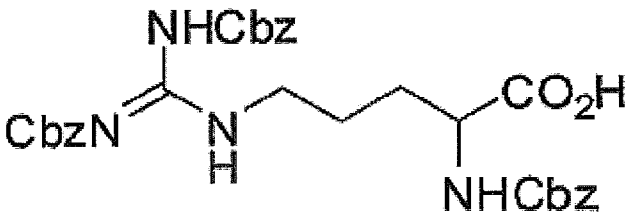
producing a tri-carbobenzoxy-arginine amine salt in a solid form by the method as described herein; and

adding an acid to the tri-carbobenzoxy-arginine amine to extract a tri-carbobenzoxy-arginine in an organic layer.

[0010e] In another aspect, there is provided a method for producing a tri-carbobenzoxy-arginine, comprising:

producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a

solid form,



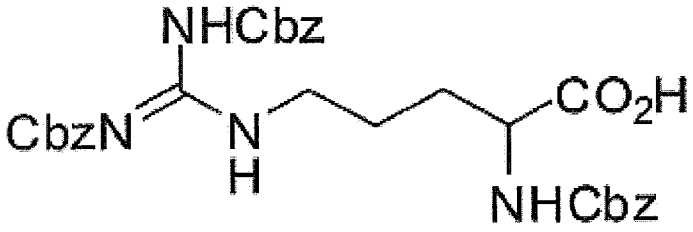
$NR^2R^3R^4$ (3)

,

wherein R^2, R^3 and R^4 each is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

by the following the method comprising:

adding an amine to a tri-carbobenzoxy-arginine of the formula (2):



(2)

such that the tri-carbobenzoxy-arginine amine salt is obtained, and

filtering the obtained tri-carbobenzoxy-arginine amine salt, and

adding an acid to the tri-carbobenzoxy-arginine amine salt to extract a tri-carbobenzoxy-arginine in an organic layer.

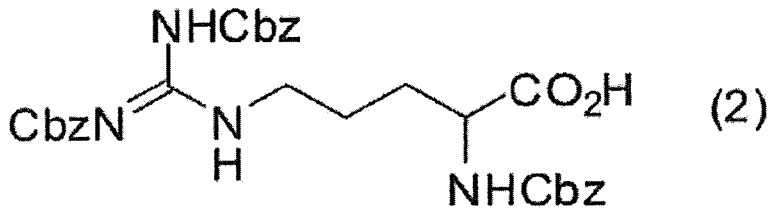
EFFECTS OF THE INVENTION

[0011]

According to the present invention, the reaction liquid has satisfactory

CLAIMS

1. A method for producing a tri-carbobenzoxy-arginine of the formula (2):



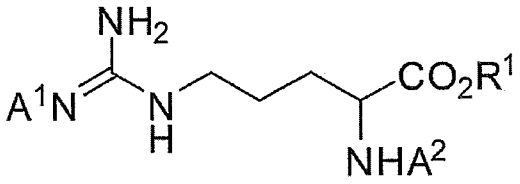
(2)

,

wherein Cbz represents a benzyloxycarbonyl group,

the method comprising:

adding carbobenzoxy chloride and a base in the presence of a surfactant to an arginine or arginine derivative of the formula (1) or a salt thereof:



(1)

,

wherein A^1 and A^2 each represents an amino group protecting group or a hydrogen atom, and R^1 represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent, such that the arginine or arginine derivative of the formula (1) or a salt thereof is carbobenzoxylated,

wherein, in the adding, the carbobenzoxy chloride and the base are added to the arginine or arginine derivative of the formula (1) or a salt thereof in a bilayer system comprising water and an organic solvent, and

wherein the surfactant is selected from the group consisting of a carboxylic acid-type surfactant, a sulfonic acid-type surfactant, a sulfuric acid ester-type surfactant, a phosphoric acid ester-type surfactant and a quaternary ammonium salt-type surfactant.

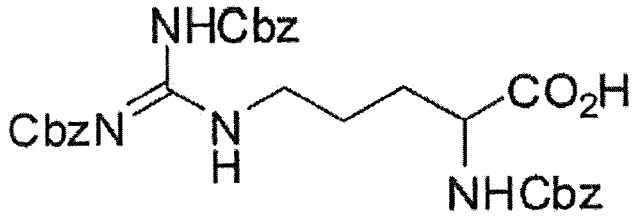
2. The method according to claim 1, wherein the base is an alkali metal hydroxide.

3. The method according to claim 1, wherein the arginine or arginine derivative of the formula (1) is an arginine or arginine hydrochloride.

4. The method according to claim 1, further comprising:

deprotecting and carbobenzoxylating the amino group protecting group of A^1 or A^2.

5. A method for producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a solid form,



$NR^2R^3R^4$ (3)

,

wherein R^2, R^3 and R^4 each represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

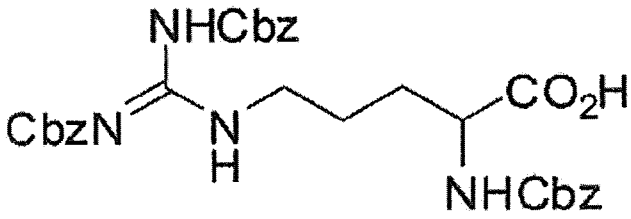
the method comprising:

producing a tri-carbobenzoxy-arginine by the method according to claim 1; and

adding an amine to a solution comprising the tri-carbobenzoxy-arginine such that the tri-carbobenzoxy-arginine amine salt in a solid form is obtained.

6. A method for producing a tri-carbobenzoxy-arginine, comprising:

producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a solid form



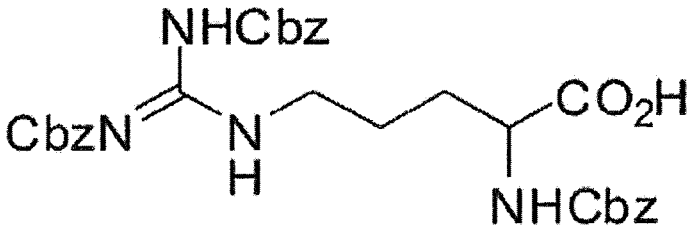
$NR^2R^3R^4$ (3)

,

wherein R^2, R^3 and R^4 each represents a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

by the following method comprising:

adding an amine to a tri-carbobenzoxy-arginine of the formula (2):



(2)

such that the tri-carbobenzoxy-arginine amine salt is obtained, and

isolating the obtained tri-carbobenzoxy-arginine amine salt,

and

adding an acid to the tri-carbobenzoxy-arginine amine salt to extract a tri-carbobenzoxy-arginine in an organic layer.

7. A method for producing a tri-carbobenzoxy-arginine, comprising:

producing a tri-carbobenzoxy-arginine amine salt in a solid form by the method according to claim 5; and

adding an acid to the tri-carbobenzoxy-arginine amine to extract a tri-carbobenzoxy-arginine in an organic layer.

8. The method according to claim 1, wherein A^1 and A^2 in the formula (1) each is a hydrogen atom.

9. The method according to claim 1, wherein the organic solvent comprises at least one selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate, tert-butyl methyl ether, ethylene glycol dibutyl ether, dichloromethane, chloroform, 1,2-dichloroethane, toluene, chlorobenzene, and xylene.

10. The method according to claim 1, wherein the bilayer system comprises from 1 to 10 parts by weight of water with respect to 1 part by weight of the organic solvent.

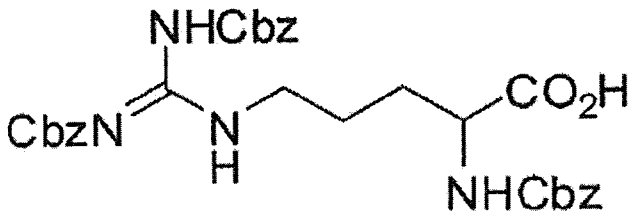
11. The method according to claim 1, wherein, in the adding, 32 mol or less of the carbobenzoxy chloride is added with respect to 1 mol of the arginine or arginine derivative of the formula (1) or a salt thereof.

12. The method according to claim 1, wherein the adding comprises simultaneously and continuously adding the carbobenzoxy chloride and the base to the arginine or arginine derivative of the formula (1) or a salt thereof.

13. The method according to claim 1, wherein, in the adding, the carbobenzoxy chloride and the base are added such that the arginine or arginine derivative of the formula (1) or a salt thereof is carbobenzoxylated at a temperature of from -50°C to 50°C.

14. A method for producing a tri-carbobenzoxy-arginine, comprising:

producing a tri-carbobenzoxy-arginine amine salt of the formula (3) in a solid form,



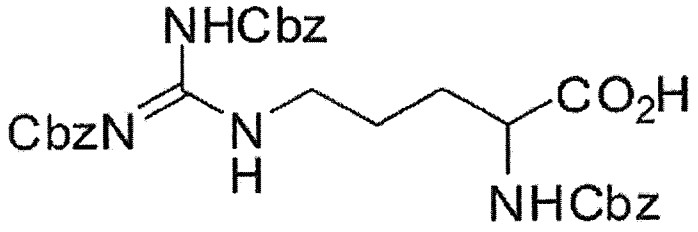
$NR^2R^3R^4$ (3)

,

wherein R^2, R^3 and R^4 each is a hydrogen atom, an alkyl group having 1 to 6 carbon atoms optionally having a substituent, or an aralkyl group having 7 to 15 carbon atoms optionally having a substituent,

by the following the method comprising:

adding an amine to a tri-carbobenzoxy-arginine of the formula (2):



(2)

such that the tri-carbobenzoxy-arginine amine salt is obtained, and

filtering the obtained tri-carbobenzoxy-arginine amine salt, and

adding an acid to the tri-carbobenzoxy-arginine amine salt to extract a tri-carbobenzoxy-arginine in an organic layer.