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(54) **Title:** A PROCESS FOR PREPARATION OF MEROPENEM

(57) **Abstract:** The present invention relates to a novel, cost-effective process for the preparation of Sterile Meropenem Trihydrate, which is prepared by a) condensation of 1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3- [(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl) methyl ester, [4R-[4a,5b,6b(R*)]] with (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxycarbonyl)-1-pyrrolidine to obtain diprotected Meropenem; b) deprotection and hydrogenation of diprotected Meropenem to obtain non-sterile Meropenem Trihydrate; c) conversion of NS Meropenem Trihydrate into Sterile Meropenem Trihydrate by using water, methanolic ammonia solution and purging carbon dioxide gas.



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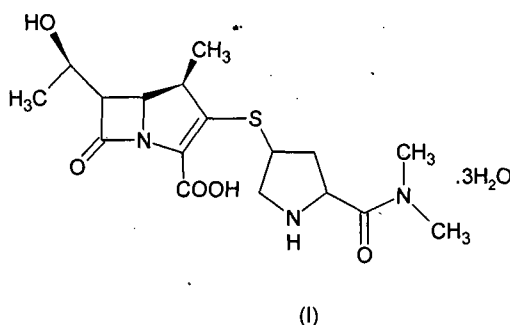
A Process for Preparation of Meropenem

FIELD OF INVENTION

The present invention relates to a novel, cost-effective process for the preparation of Meropenem Trihydrate, which is prepared by condensation of enol-phosphate ester with thiol derivative, particularly 1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl)methyl ester, [4R-[4a,5b,6b(R*)]] (MAP) with (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxycarbonyl)-1-pyrrolidine (Meropenem side chain) followed by deprotection and purification to give Sterile Meropenem Trihydrate with improved yield and quality.

BACKGROUND OF THE INVENTION

Meropenem Trihydrate is a beta-lactam antibiotic and belongs to the subgroup of carbapenem. It is chemically known as (4R,5S,6S)-3-[[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate and represented by the following structural formula I.



Meropenem trihydrate is an ultra-broad spectrum injectable antibiotic used to treat a wide variety of infections, including pneumonia, urinary tract infections, intra-abdominal, gynaecological, skin, and soft tissue infections, meningitis, septicaemia and febrile neutropenia.

There are number of literatures available which describe the process for preparation of Meropenem trihydrate. Meropenem was originally developed by

Sumitomo Pharmaceuticals and reported in US4,943,569A. This patent describes a process for its preparation, in which (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3,2,0]-hept-3,7-dione-2-carboxylate was dissolved in dry acetonitrile and diisopropylethylamine and treated with diphenyl chlorophosphate and [2S,4S]-1-p-nitrobenzyloxycarbonyl-2-dimethylaminocarbonyl-4-mercaptopyrrolidine. The obtained diprotected compound was dissolved in a mixture of tetrahydrofuran and ethanol, and the mixture was hydrogenated in a morpholinopropanesulfonic acid buffer solution in presence of 10% palladium-carbon, and then subjected to polymer chromatography to obtain Meropenem.

US 4,888,344A describes an improved process for preparing Meropenem trihydrate from diprotected compound in THF and water, followed by addition of 10% palladium-carbon to obtain Meropenem Trihydrate.

WO 2007029084A2 provides a process for the preparation of Meropenem trihydrate by condensing 4-nitrobenzyl (4R, 5S, 6S)-3-[(diphenoxyphosphoryl)oxy]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and 4-nitrobenzyl (2S,4S)-2-[(dimethylamino)carbonyl]-4-mercaptopyrrolidine-1-carboxylate in DMF and treating with diisopropylethylamine. The obtained reaction mixture was poured into mixture of ethyl acetate and water; and hydrogenated with mixture of 5% Pd/C in aq. buffer containing N-methylmorpholine and acetic acid. The reaction mixture was filtered, and aq. layer was concentrated by reverse osmosis and THF was added to obtain Meropenem Trihydrate.

WO 2006035300A2 discloses a process for the preparation of Meropenem trihydrate comprising crystallization of Meropenem by using acetone at 0-5°C, and further washing with chilled acetone to obtain pure Meropenem trihydrate.

US 20090264643A1 describes a process for the preparation of sterile Meropenem trihydrate comprising the condensation of 4-nitrobenzyl (4R, 5S, 6S)-3-[(diphenoxyphosphoryl)oxy]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and 4-nitrobenzyl (2S,4S)-2-[(dimethylamino)carbonyl]-4-mercaptopyrrolidine-1-carboxylate in acetonitrile and treatment with diisopropylethylamine. The obtained reaction mass was

quenched into ethyl acetate containing dipotassium hydrogen orthophosphate buffer to obtain diprotected Meropenem, which is further hydrogenated with 10% Pd/C to obtain Meropenem non-sterile. This non-sterile Meropenem is dissolved in water and ammonia solution, treated with carbon and filtered by micron filter. The pH was adjusted and anti-solvent THF was added to obtain pure sterile Meropenem.

Most of the prior art process as described above uses phosphate buffer solution for isolation of diprotected compound which increases the effluent treatment load and the obtained compound has presence of Phosphate salt. The prior art process also uses ammonia solution for dissolution of Meropenem non-sterile which doesn't allow the same at lower temperature where degradation can be minimized. The prior art process uses anti-solvents or seeding for the isolation of Meropenem sterile.

Thus it is highly desirable to develop a process which avoids the use of phosphate buffer solution for isolation of diprotected compound, use of ammonia solution for dissolution of Meropenem non-sterile and use of anti-solvents or seeding for the isolation of Meropenem sterile. The present inventors have developed a very cost effective and environment friendly process which avoids these three things.

SUMMARY OF THE INVENTION

The principal aspect of the present invention is to provide a process for the preparation of sterile Meropenem trihydrate comprising:

- a) dissolving Meropenem or its hydrate in water in the presence of an alcoholic base and in the presence or absence of solvent;
- b) optionally filtering through micron filter;
- c) adjusting the pH to 4.5 to 6.5; and
- d) optionally washing with solvent to yield sterile Meropenem trihydrate.

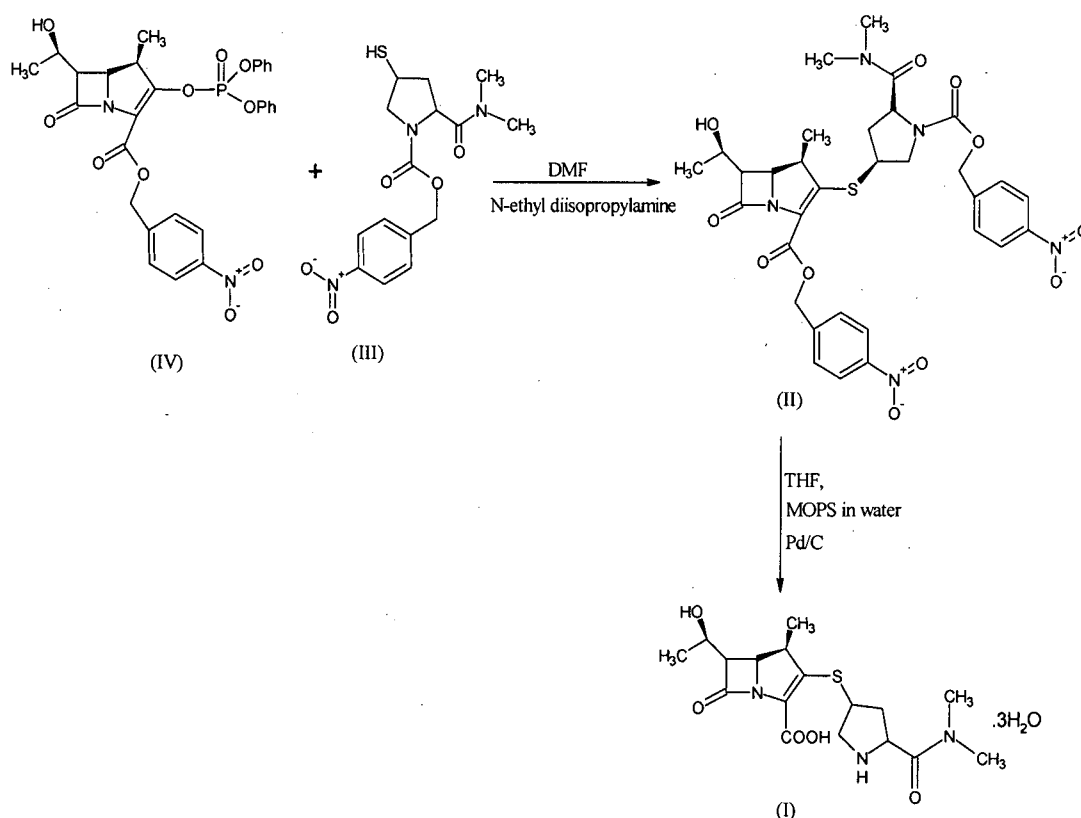
Another aspect of the present invention is to provide a process for preparation of Meropenem trihydrate of formula (I) comprising:

- a) reacting 1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl) methyl ester, [4R-[4a,5b,6b(R*)]] of formula (IV) with

- (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxycarbonyl)-1-pyrrolidine of formula (III) in a suitable solvent and a base to yield diprotected Meropenem of formula (II);
- b) isolating the diprotected Meropenem of formula (II) by quenching in carbonated water;
- c) deprotecting the diprotected Meropenem of formula (II) in a suitable solvent and a buffer in water, followed by hydrogenation to obtain non-sterile Meropenem trihydrate of formula (I) and
- d) optionally converting non-sterile Meropenem trihydrate into sterile Meropenem trihydrate by using a solvent and alcoholic ammonia solution in presence of carbon dioxide.

The process of the present invention may be illustrated as in below scheme:

Scheme 1



DETAIL DESCRIPTION OF THE INVENTION

Accordingly in an embodiment of the invention, alcoholic bases in step (a) is a methanolic or ethanolic solution of base selected from the group consisting of ammonia, sodium hydroxide, sodium carbonate, potassium carbonate, diethylamine, diisopropylamine, triethylamine, diisopropylethylamine, sodium bicarbonate, potassium bicarbonate, sodium acetate, sodium-2-ethyl hexanoate, sodium lactate and the like, preferably methanolic ammonia.

In another embodiment of the invention, solvent used in step (a) for dissolving Meropenem, is selected from the group consisting of acetone, methanol, ethanol, isopropanol, 1-propanol, THF, acetonitrile or mixtures thereof, preferably methanol.

In another embodiment of the invention, pH in step (c) is adjusted to 4 to 7 preferably 4.5 to 6.5 and most preferably 5.5 to 6 by an acid selected from the group consisting of formic acid, hydrochloric acid, sulfuric acid, phosphoric acid and acetic acid preferably by formic acid.

In still another embodiment of the invention, the above obtained reaction mixture may be treated with carbon and/or with a chelating agent like ethylene diamine tetraacetic acid (EDTA). The obtained crystallized Meropenem trihydrate obtained in step (c) is washed with a solvent selected from the group consisting of acetone, methanol, ethanol, isopropanol (IPA), n-propanol, methylethylketone(MEK), methyl isobutyl ketone (MIBK) or methyl tert-butyl ketone(MTBK), preferably with acetone and dried under vacuum to obtain Sterile Meropenem trihydrate. It is to be noted that in the present invention neither any anti-solvent nor seeding is used for the precipitation of the sterile Meropenem.

In still further embodiment of the invention, the suitable solvent in step (a) for the reaction of 1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl) methyl ester,[4R-[4a,5b,6b(R*)]] of formula (IV) and (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxycarbonyl)-1-pyrrolidine of formula (III) is selected from the group consisting of tetrahydrofuran, dichloromethane, acetone, dimethylformamide, acetonitrile preferably dimethylformamide and base is selected from the group consisting of

secondary amine such as diisopropylamine, dicyclohexylamine or a tertiary amine such as 4-dimethylaminopyridine, N-ethyl-diisopropylamine, triethylamine, tetramethylguanidine (TMG) and tributylamine preferably N-ethyl-diisopropylamine. The reaction is carried out at -50 °C to -20 °C, preferably at -25 °C to -35 °C.

In still further embodiment of the invention, the suitable solvent in step (c) for deprotection of diprotected Meropenem is selected from the group comprising acetone, N,N-dimethylformamide, tetrahydrofuran (THF), ethanol, methanol, acetonitrile, preferably tetrahydrofuran and the buffer selected from the group consisting of dipotassium hydrogen orthophosphate, potassium dihydrogen orthophosphate, and 3-morpholinopropane-1-sulfonic acid. The buffer is preferably 3-morpholinopropane-1-sulfonic acid.

In another embodiment of the invention, the hydrogenation in step (c) is preferably carried out at 25°C - 30°C using a catalyst selected from platinum oxide, palladium on carbon (Pd/C), platinum on carbon (Pt/C) preferably palladium on carbon.

In still another embodiment of the invention, the starting materials used in this invention are commercially available and can be made by the process available in the literature.

Some of the advantages of present invention are stated below:

- a) The present invention uses carbonated water for the isolation of diprotected Meropenem of formula (II) in step (b) which reduces effluent treatment load significantly and avoids the presence of phosphate salt in the compound to give better quality of the product.
- b) Diprotected Meropenem was isolated at the pH of 6 to 6.5 by purging carbon dioxide gas.
- c) For the preparation of sterile Meropenem, the present invention uses methanolic ammonia, which facilitates dissolution at lower temperature at -10 °C. At lower temperature the degradation of Meropenem is minimized.

- d) The present invention avoids the use of anti-solvent or seeding for the precipitation of sterile Meropenem, which makes the reaction further cost effective.

The present invention can be illustrated by the following examples, which are not to limit the scope of invention.

Example 1: Preparation of Non-Sterile (NS) Meropenem

(a) Process for the preparation of Diprotected Meropenem.

1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl)methyl ester,[4R-[4a,5b,6b(R*)]] (MAP) (25g) and (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxycarbonyl)-1-pyrrolidine (16g) were dissolved in DMF (125 ml), stirred at -25°C to -30°C and cooled to -30°C to -35°C. N-ethyldiisopropylamine (7g) was added to the above reaction mass and stirred at -25°C to -30°C. The reaction mass was quenched into Carbonated water (500ml) at 6.0 to 6.5 pH and stirred at 0°C to 5°C. The solid was filtered and washed with DM water. The wet solid was taken for the next step.

Yield: 125 – 140 g

(b) Process for the preparation of Non-Sterile (NS) Meropenem.

Diprotected Meropenem was dissolved in tetrahydrofuran (500ml) at 25°C. It was added to an aqueous solution of 3-morpholinopropane-1-sulfonic acid of pH 6.0-6.5. (The aqueous solution of 3-morpholinopropane-1-sulfonic acid is prepared by adding 3-morpholinopropane-1-sulfonic acid (15g) in purified water (210 ml) at 25°C- 30°C and pH is adjusted by N-methyl morpholine). The reaction mixture was charged into autoclave and stirred under hydrogen pressure in presence of palladium on carbon at 25°C- 30°C. The reaction mass was filtered and filtrate was washed with methylene dichloride (475 ml). The aqueous layer was treated with carbon at 25°C- 30°C and degaussed under vacuum. The reaction mixture was filtered and to

the filtrate acetone was added and stirred at 0°C- 5°C, filtered, washed with chilled acetone and dried.

Yield: 12-13g.

Example 2: Preparation of Sterile Meropenem trihydrate

A. Non sterile Meropenem was charged into methanol (20 ml) and purified water (70 ml) at 0°-5°C. 12% Methanolic ammonia solution was added into it and pH was adjusted to 9.0-9.5 at -5°C to -10°C and stirred. Carbon dioxide gas was purged to reduce the pH 7.0 to 8.5. The reaction mass was treated with carbon and ethylene diamine tetraacetic acid at -5°C to -10°C and filtered. The pH of the filtrate was adjusted to 5.5 to 6.0 using 10-12% formic acid (9 ml) at -5°C to -10°C. The filtrate was further stirred for 2 hours at -5°C to -10°C. The solid was filtered and washed with acetone and dried to obtain sterile Meropenem trihydrate.

Yield: 8.7 to 9.0g

B. Non sterile Meropenem was charged into methanol (20 ml) and purified water (70 ml) at 0°-5°C. 12% Methanolic ammonia solution was added into it and pH was adjusted to 9.0-9.5 at -5°C to -10°C and stirred. Carbon dioxide gas was purged to reduce the pH 7.0 to 8.5. The reaction mass was treated with carbon and ethylene diamine tetraacetic acid at -5°C to -10°C and filtered. The pH of the filtrate was adjusted to 5.5 to 6.0 using 10-12% formic acid (9 ml) at 15°C. The filtrate was stirred for 1 hour at 15°C and further stirred for another hour at 5°C. The solid was filtered and washed with acetone and dried to obtain sterile Meropenem trihydrate.

Yield: 8.5 to 8.7g

C. Non sterile Meropenem was charged into methanol (20 ml) and purified water (70 ml) at 0°-5°C. 12% Methanolic ammonia solution was added into it and pH was adjusted to 9.0-9.5 at -5°C to -10°C and stirred. Carbon dioxide gas was purged to reduce the pH 7.0 to 8.5. The reaction mass was

treated with carbon and ethylene diamine tetraacetic acid at -5°C to -10°C and filtered. The pH of the filtrate was adjusted to 5.5 to 6.0 using 10-12% formic acid (9 ml) at 15°C. The filtrate was stirred for 1 hour at 15°C and for further another hour at -5°C and again for one hour at 15°C. The solid was filtered and washed with acetone and dried to obtain sterile Meropenem trihydrate.

Yield: 8.7 to 9.0g

- D. Non sterile Meropenem(10gm) was charged into methanol (20 ml) and purified water (70 ml) at 0°-5°C. 12% Methanolic ammonia solution was added into it and pH was adjusted to 9.0-9.5 at -5°C to -10°C and stirred. Carbon dioxide gas was purged to reduce the pH 7.0 to 8.5. The reaction mass was treated with carbon and ethylene diamine tetraacetic acid at -5°C to -10°C and filtered. Carbon dioxide gas was purged to reduce the pH 6.5 to 6.0 to obtained product precipitated from medium after stirring 1hr, further pH was adjusted to 5.5 to 6.0 using 10-12% formic acid at 15°C. The solid was stirred for 1 hour at 15°C and for further another hour at -5°C and again for one hour at 15°C. The solid was filtered and washed with acetone and dried to obtain sterile Meropenem trihydrate.

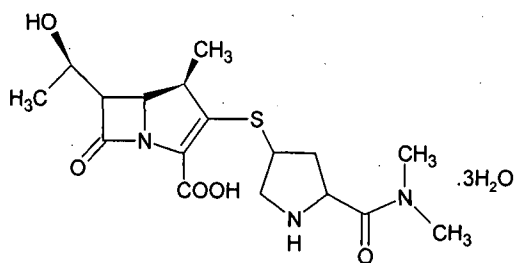
Yield: 8.8 to 9.2g

- E. Non sterile Meropenem(10gm) was charged into methanol (20 ml) and purified water (70 ml) at 0°-5°C. 12% Methanolic ammonia solution was added into it and pH was adjusted to 9.0-9.5 at -5°C to -10°C and stirred. Carbon dioxide gas was purged to reduce the pH 7.0 to 8.5. The reaction mass was treated with carbon and ethylene diamine tetraacetic acid at -5°C to -10°C and filtered. Carbon dioxide gas was purged to reduce the pH 6.5 to 6.0 to obtained product precipitated from medium after stirring 1hr, further pH was adjusted to 5.5 to 6.0 using 10-12% formic acid at 15°C. The solid was stirred for 1 hour at 15°C and for further another hour at -5°C and again for one hour at 15°C. The solid was filtered and washed with methanol and dried to obtain sterile Meropenem trihydrate.

Yield: 8.0 to 8.5g

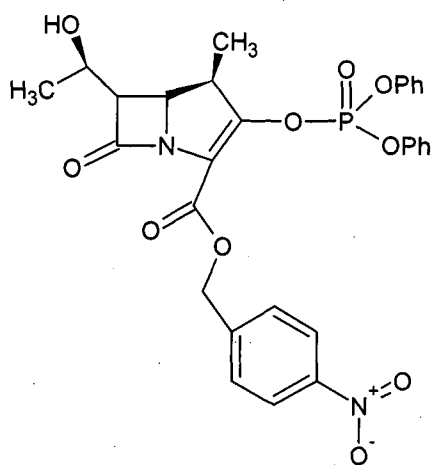
We claim:

1. A process for the preparation of sterile Meropenem trihydrate comprising:
 - a) dissolving Meropenem or its hydrate in water in the presence of an alcoholic base and in the presence or absence of solvent;
 - b) optionally filtering through micron filter;
 - c) adjusting the pH to 4.5 to 6.5; and
 - d) optionally washing with solvent to yield sterile Meropenem trihydrate.
2. A process according to claim 1, wherein alcoholic base in step (a) is a methanolic or ethanolic solution of base selected from the group consisting of ammonia, sodium hydroxide, sodium carbonate, potassium carbonate, diethylamine, diisopropylamine, triethylamine, diisopropylethylamine, sodium bicarbonate, potassium bicarbonate, sodium acetate, sodium-2-ethyl hexanoate and sodium lactate.
3. A process according to claim 1, wherein solvent in step (a) for dissolving Meropenem, is selected from the group consisting of acetone, methanol, ethanol, isopropanol, 1-propanol, THF, acetonitrile or mixtures thereof.
4. A process according to claim 1, wherein pH in step (c) is adjusted by an acid selected from the group consisting of formic acid, hydrochloric acid, sulfuric acid, phosphoric acid and acetic acid.
5. A process according to claim 1, wherein the solvent for optional washing in step (d) is selected from the group consisting of acetone, methanol, ethanol, isopropanol, n-propanol, methylethylketone, methyl isobutyl ketone and methyl tert-butyl ketone.
6. A process for the preparation of sterile Meropenem trihydrate of formula (I) comprising:

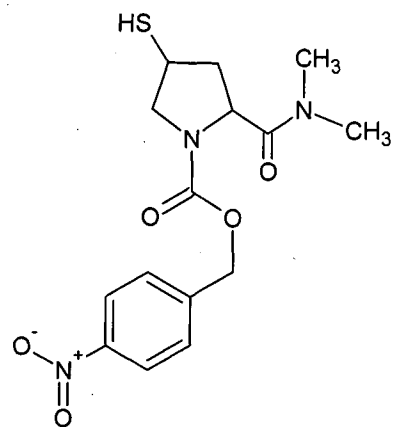


(I)

- a) reacting 1-Azabicyclo[3.2.0]hepta-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrobenzyl) methyl ester, [4R-[4a,5b,6b(R*)]] of formula (IV) with (2S,4S)-2-(Dimethylaminocarbonyl)-4-mercapto-1-(p-nitrobenzyloxy carbonyl)-1-pyrrolidine of formula (III) in a suitable solvent and a base to yield diprotected Meropenem of formula (II);

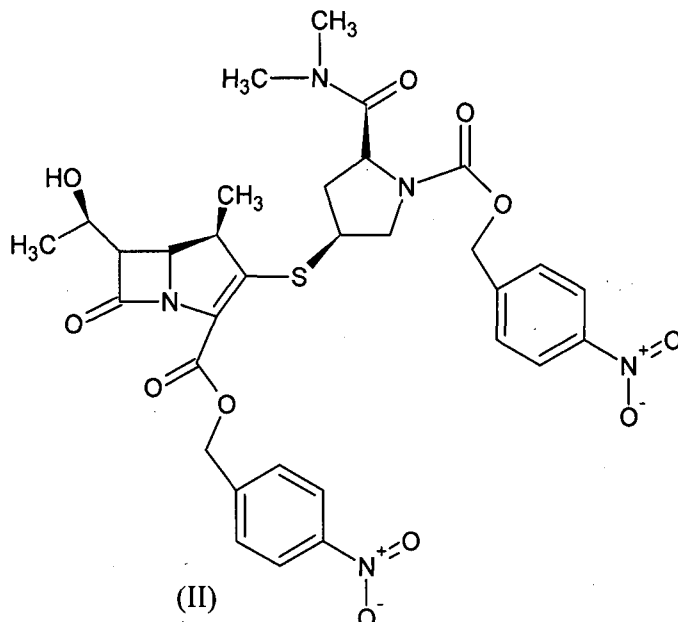


(IV)



(III)

- b) isolating the diprotected Meropenem of formula (II) by quenching in carbonated water;



- c) deprotecting the diprotected Meropenem of formula (II) in a suitable solvent and a buffer in water, followed by hydrogenation to obtain Meropenem trihydrate NS of formula (I) and
 - d) optionally converting NS Meropenem trihydrate into sterile Meropenem trihydrate by using a solvent and alcoholic ammonia solution in presence of carbon dioxide.
7. A process according to claim 6, wherein for the suitable solvent in step (a) is selected from the group consisting of tetrahydrofuran, dichloromethane, acetone, dimethylformamide and acetonitrile and the base is selected from a group consisting of diisopropylamine, dicyclohexylamine, 4-dimethylaminopyridine, N-ethyldiisopropylamine, triethylamine, tetramethylguanidine (TMG) and tributylamine.
 8. A process according to claim 6, wherein for the suitable solvent in step (a) is dimethylformamide and the base is N-ethyldiisopropylamine.
 9. A process according to claim 6, wherein the suitable solvent in step (c) is selected from the group comprising acetone, N,N-dimethylformamide, tetrahydrofuran (THF), ethanol, methanol, acetonitrile and the buffer is selected from the group consisting of dipotassium hydrogen orthophosphate, potassium dihydrogen orthophosphate, and 3-morpholinopropane-1-sulfonic acid.

10. A process according to claim 6, wherein the suitable solvent in step (c) is tetrahydrofuran and the buffer is 3-morpholinopropane-1-sulfonic acid.
11. A process according to claim 6, wherein hydrogenation in step (c) carried out at 25 °C-30 °C using a catalyst selected from platinum oxide, palladium on carbon, Platinum on carbon.
12. A process according to claim 6, wherein hydrogenation in step (c) carried out using a catalyst palladium on carbon.
13. A process according to claim 6, wherein non-sterile Meropenem trihydrate in step (d) is dissolved in methanol, water and methanolic ammonia solution to convert to sterile Meropenem trihydrate.
14. A process according to claim 6, wherein for conversion of non-sterile Meropenem to sterile Meropenem trihydrate in step (d), the pH is adjusted to 7.0 to 8.5 by using carbon dioxide and further adjusted to 5.5-6.0 by an acid selected from the group consisting of formic acid, hydrochloric acid, sulfuric acid, phosphoric acid and acetic acid.
15. A process according to claim 6, wherein non-sterile Meropenem trihydrate obtained in step (d) is washed with acetone, methanol, ethanol, isopropanol, n-propanol, methylethylketone, methyl isobutyl ketone or methyl tert-butyl ketone.