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

(57) Abstract: The present invention provides a one-pot process for the preparation of meropenem. The present invention further provides a process for the preparation of meropenem trihydrate.



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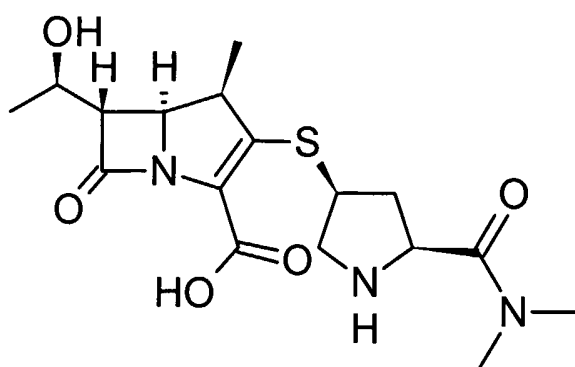
A PROCESS FOR THE PREPARATION OF MEROPENEM

Field of the Invention

The present invention provides a one-pot process for the preparation of meropenem. The present invention further provides a process for the preparation of meropenem trihydrate.

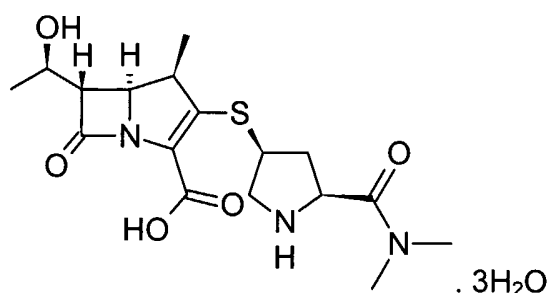
Background of the Invention

(4R,5S,6S)-3-[[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxy-ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, commonly known as meropenem (Formula I) is a synthetic, broad-spectrum, carbapenem antibiotic. Administration of meropenem is indicated as single-agent therapy for the treatment of the following infections when caused by the following susceptible strains: complicated appendicitis and peritonitis caused by viridians group *Streptococci*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus* species; bacterial meningitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (b-lactamase and non-b-lactamase-producing strains), and *Neisseria meningitidis*. Meropenem has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis. Meropenem is commercially available as a crystalline trihydrate form having Formula II.



FORMULA I

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**FORMULA II**

U.S. Patent No. 4,888,344 provides a process for the preparation of the crystalline trihydrate of meropenem. U.S. Patent Nos. 4,943,569 and 5,122,604 provide similar processes for the preparation of meropenem trihydrate. Sunagawa et al., *J. Antibiotics*, XLIII, 1176 (1990) discusses several methods for preparation of carbapenem derivatives, specifically meropenem.

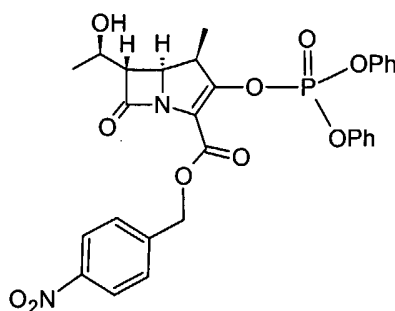
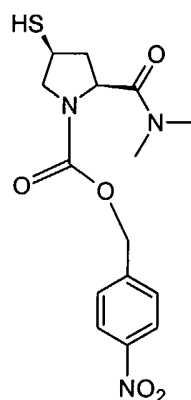
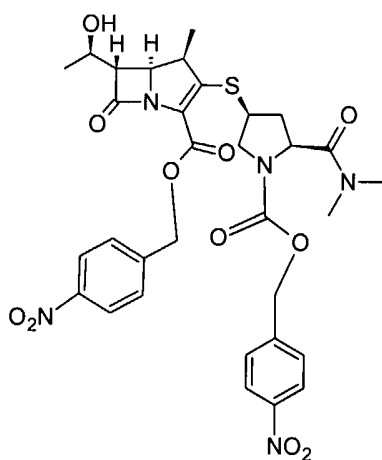
The processes reported in the prior art are time-consuming, costly and not commercially scalable. This is especially because of the column chromatographic purification of intermediates, the isolation of intermediates at every stage and use of costly reagents. Hence, there is a need to provide simple, cost-effective and easily scalable process for the preparation of meropenem.

Further, the processes reported in the prior art provide meropenem trihydrate which involves lyophilization of an aqueous layer containing meropenem. The amorphous material so obtained is crystallized to get meropenem trihydrate. Alternatively the process involves column chromatographic purification of reaction product followed by concentration of the aqueous layer by reverse osmosis. To the concentrated aqueous layer, acetone or tetrahydrofuran or isopropanol is added for the precipitation of meropenem trihydrate. The yield of meropenem trihydrate thus obtained is generally low, and the purity is variable.

Summary of the Invention

The present inventors have found that meropenem can be prepared by condensation reaction of the enol-phosphate of Formula III with thiopyrrolidine of Formula IV to produce the compound of Formula V, and deprotection the compound of Formula V without isolation to obtain meropenem.

- 3 -

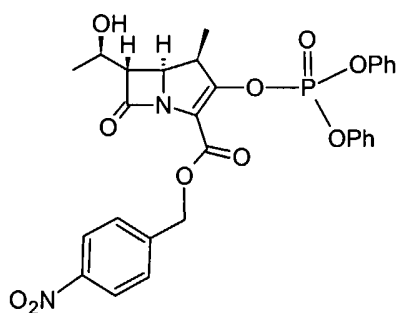
**FORMULA III****FORMULA IV****FORMULA V**

The present inventors have further found that meropenem trihydrate can be isolated from the aqueous reaction layer without any chromatographic purification or reverse osmosis technique, rather by adding water miscible co-solvents such as acetone, tetrahydrofuran or isopropanol. The processes of the present invention are high-yielding, cost-effective and easily scalable at commercial scale. Meropenem trihydrate obtained according to processes described herein has a purity in excess of 98% w/w when measured by HPLC.

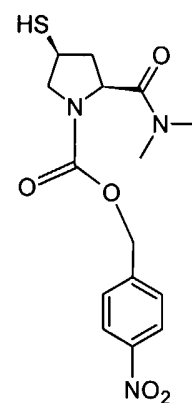
Detailed Description of the Invention

In one aspect, a one-pot process for preparation of meropenem is provided, which comprises:

- 5 a) condensing an enol-phosphate of Formula III with the thiopyrrolidine of Formula IV to produce the protected product of Formula V,

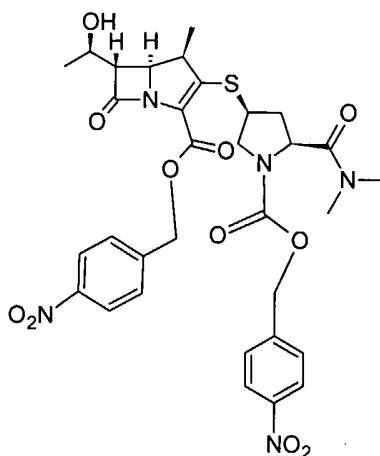


FORMULA II **I**



FORMULA IV

- b) deprotecting the compound of Formula V by hydrogenolysis, and



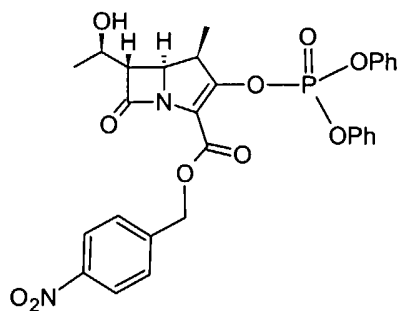
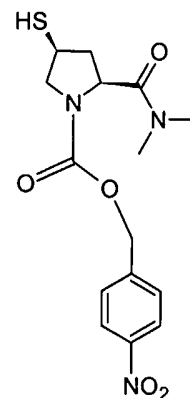
FORMULA V

- c) isolating meropenem from the reaction mass thereof,
in particular, the compound of Formula V is not isolated before deprotection.

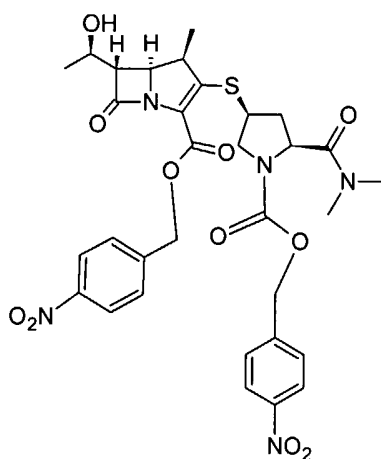
15 In another aspect, processes for preparation of meropenem are provided, which comprises:

- 5 -

- a) condensing an enol-phosphate of Formula III with the thiopyrrolidine of Formula IV to produce the compound of Formula V,

**FORMULA II****FORMULA IV**

- b) deprotecting the compound of Formula V by hydrogenolysis, characterized by the deprotection being carried out in a biphasic system, and

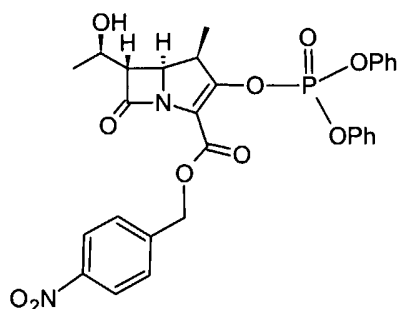
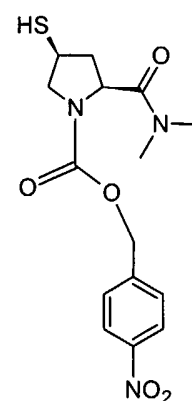
**FORMULA V**

- c) isolating meropenem from the reaction mass thereof.

In a further aspect, processes for preparation of meropenem are provided which comprises:

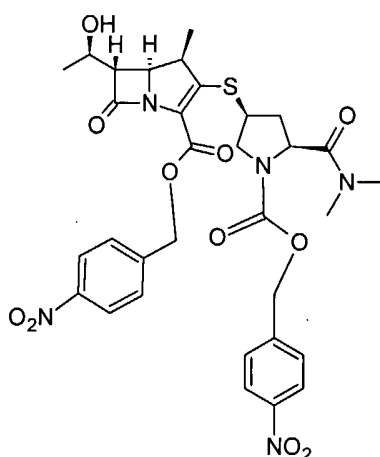
- a) condensing enol-phosphate of Formula III with thiopyrrolidine of Formula IV to produce the compound of Formula V,

- 6 -

**FORMULA II****FORMULA IV**

- b) deprotecting the compound of Formula V by hydrogenolysis characterized by the fact that N-methylmorpholine and an acid is used as a buffering agent,

5

**FORMULA V**

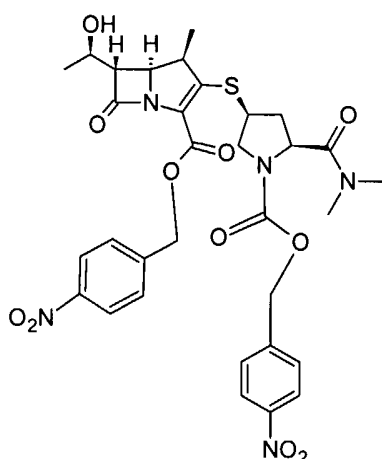
- c) isolating meropenem from the reaction mass thereof.

In yet another aspect, processes for the preparation of meropenem trihydrate are provided which comprises:

10

- a) deprotecting the compound of Formula V by hydrogenolysis,

- 7 -

**FORMULA V**

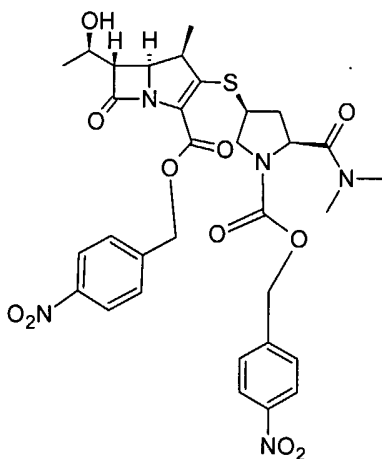
b) separating the aqueous layer containing meropenem from the reaction mass,

5 c) adding a water miscible organic solvent to the aqueous layer to precipitate meropenem trihydrate from the aqueous solution, and

d) isolating pure meropenem trihydrate from the reaction mass thereof.

In still a further aspect, meropenem trihydrate having purity greater than 98% is provided, prepared by a process comprising

10 a) deprotecting the compound of Formula V by hydrogenolysis,

**FORMULA V**

b) separating the aqueous layer containing meropenem from the reaction mass,

- 8 -

- c) adding a water miscible organic solvent to the aqueous layer to precipitate meropenem trihydrate from the aqueous solution, and
- d) isolating meropenem trihydrate having purity greater than 98% from the reaction mass thereof.

5 Enol-phosphate of Formula III and thiopyrrolidine of Formula IV can be prepared by processes reported in the prior art. These two compounds can be dissolved in an organic solvent and the resultant reaction mass under stirring may be cooled to about -60° to -10°C. The organic solvent may be inert and may keep the reactants substantially in solution when cooled. To this reaction mass is added diisopropylamine dropwise to
10 control the temperature. After stirring from about 30 minutes to about 6 hours, the reaction mixture can be poured in a mixture of ethyl acetate and water.

Following separation of the layers, the organic layer is directly subjected to hydrogenolysis for deprotection of the protecting groups. Water is added to the organic layer containing the product and the resultant biphasic mass is hydrogenated using a noble
15 metal catalyst. For this purpose, hydrogen gas or a compound capable of generating hydrogen gas can be used as source of hydrogen. Additionally, to the reaction mass a buffering agent comprising N-methylmorpholine and an acid may be added. The acid to be used could be an organic or an inorganic acid.

Hydrogenation carried out in a biphasic system offers several advantages. Firstly,
20 side products such as p-toluidine and coloring impurities remain in the organic layer whereas deprotected meropenem is present in aqueous layer. Secondly, isolation of meropenem from aqueous layer is easy, as removal of impurities present in organic layer is facilitated by layer separation. Use of N-methylmorpholine and an acid as a buffer offers advantage in terms of cost and availability. The buffer system also serves as a tool
25 for carrying out the reaction at a pH of about 7.

After completion of the reaction, the aqueous layer containing the product is washed with an organic solvent and to the combined aqueous layers is added a miscible organic solvent so as to precipitate meropenem trihydrate from the solution thereof. The precipitation can be carried out at lower temperature of about -20 to 25°C. The separated
30 meropenem trihydrate is then isolated by means of filtration or centrifuge and dried suitably to get pure meropenem trihydrate having purity in excess of 98%.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Example 1: Synthesis of Meropenem

5 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-[(diphenoxyphosphoryl)oxy]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (enol-phosphate of Formula III, 50 gm) and 4-nitrobenzyl (2*S*,4*S*)-2-[(dimethylamino)carbonyl]-4-mercaptopyrrolidine-1-carboxylate (thiopyrrolidine of Formula IV, 30 gm) was dissolved in a mixture of N,N-dimethylformamide (200 ml) at ambient temperature. The solution
10 was then cooled to -45°C and to it was added diisopropylamine (11 gm) dropwise under stirring while maintaining the temperature between -50 to -45°C. After stirring the reaction mass for about 1 hour, it was poured in to a mixture of ethyl acetate (500 ml) and water (300 ml). The organic layer was separated and added to a mixture of 5% palladium on carbon (50 gm) in aqueous buffer (500 ml) containing N-methylmorpholine and acetic
15 acid (pH about 7.0). The above biphasic reaction mass was hydrogenated for 3 hours under pressure at 20-25°C. After completion of the reaction, the mixture was filtered and aqueous layer was separated. The aqueous layer was concentrated by reverse osmosis and to the condensate was added tetrahydrofuran at a temperature of about 5-10°C. The resultant mixture was stirred for about 5 hours to get crystalline meropenem trihydrate in a
20 yield of 21.6 gm.

Example 2: Synthesis of Meropenem

Step a) Preparation of 4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-((3*S*,5*S*)-5-[(dimethylamino)carbonyl]-1-[(4-nitrophenoxy)carbonyl] pyrrolidin-3-yl)thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

25 4-nitrobenzyl (4*R*,5*R*,6*S*)-3-[(diphenoxyphosphoryl)oxy]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (enol-phosphate of Formula III, 100 gm) and 4-nitrobenzyl (2*S*,4*S*)-2-[(dimethylamino)carbonyl]-4-mercaptopyrrolidine-1-carboxylate (thiopyrrolidine of Formula IV, 60 gm) was dissolved in a mixture of N,N-dimethylformamide (800 ml) at ambient temperature. The solution
30 was then cooled to -45°C and to it was added diisopropylamine (22 gm) drop-wise under stirring while maintaining the temperature between -50 to -45°C. After stirring the

reaction mass for about 1 hour, it was poured in to a mixture of ethyl acetate (1 L) and water (1 L). The organic layer was separated and under vacuum concentrated to dryness to get the title compound in a yield of 100 gm.

Step b) Preparation of (4*R*,5*S*,6*S*)-3-((3*S*,5*S*)-5-

5 [(Dimethylamino)carbonyl]pyrrolidin-3-yl}thio)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

To 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-((3*S*,5*S*)-5-[(dimethylamino)carbonyl]-1-[(4-nitrobenzyloxy)carbonyl]pyrrolidin-3-yl}thio)-6-[(1*r*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (100 gm) in ethyl acetate (1.0 L) was added a mixture of 5% palladium on carbon (50 gm) in aqueous buffer (500 ml) containing N-methylmorpholine and 35% hydrochloric acid (pH about 7.0). The above biphasic reaction mass was hydrogenated for 3 hours under pressure at 20-25°C. After completion of the reaction, the mixture was filtered and aqueous layer was separated. The aqueous layer was concentrated by reverse osmosis and to the condensate was added tetrahydrofuran at a temperature of about 5-10°C. The resultant mixture was stirred for about 5 hours to get crystalline meropenem trihydrate in a yield of 50 gm.

Example 3: Synthesis of Meropenem trihydrate

To 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-((3*S*,5*S*)-5-[(dimethylamino)carbonyl]-1-[(4-nitrobenzyloxy)carbonyl]pyrrolidin-3-yl}thio)-6-[(1*r*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (50 gm) in ethyl acetate (500 ml) was added to a mixture of 5% palladium on carbon (50 gm) in aqueous buffer (500 ml) containing N-methylmorpholine and acetic acid (pH about 7.0). The above biphasic reaction mass was hydrogenated for 3 hours under pressure at 20-25°C. After completion of the reaction, the mixture was filtered and aqueous layer was separated. The aqueous layer was extracted with ethyl acetate (300 ml). To the aqueous layer was added acetone (1.5 Lit) slowly at a temperature of about 0-5°C and the resultant mass was stirred for 3 hours at 0-5°C. The separated solids were filtered, washed with chilled acetone and dried at ambient temperature under vacuum to get meropenem trihydrate in a yield of 24.5 gm.

Example 4: Synthesis of Meropenem trihydrate

To 4-nitrobenzyl (4*R*,5*S*,6*S*)-3-((3*S*,5*S*)-5-[(dimethylamino)carbonyl]-1-[(4-nitrobenzyloxy)carbonyl]pyrrolidin-3-yl}thio)-6-[(1*r*)-1-hydroxyethyl]-4-methyl-7-oxo-1-

azabicyclo[3.2.0]hept-2-ene-2-carboxylate (100 gm) in ethyl acetate (1.0 L) was added a mixture of 5% palladium on carbon (100 gm) in aqueous buffer (1.0 L) containing N-methylmorpholine and acetic acid (pH about 7.0). The above biphasic reaction mass was hydrogenated for 3 hours under pressure at 20-25°C. After completion of the reaction, the mixture was filtered and aqueous layer was separated. The aqueous layer was extracted with ethyl acetate (500 ml). To the aqueous layer was added acetone (3.0 Lit) slowly at a temperature of about 0-5°C and the resultant mass was stirred for 3 hours at 0-5°C. The separated solids were filtered, washed with chilled acetone and dried at ambient temperature under vacuum to get meropenem trihydrate in a yield of 50 gm.

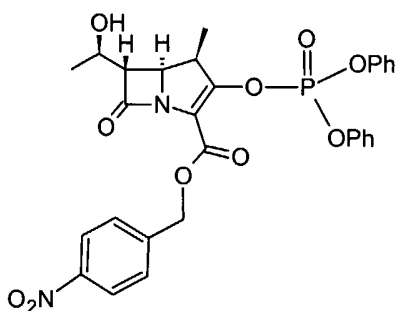
10 Example 5: Synthesis of Meropenem trihydrate

To 4-nitrobenzyl (4R,5S,6S)-3-({(3S,5S)-5-[(dimethylamino)carbonyl]-1-[(4-nitrobenzyloxyoxy)carbonyl]pyrrolidin-3-yl}thio)-6-[(1*r*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (50 gm) in ethyl acetate (500 ml) was added to a mixture of 5% palladium on carbon (50 gm) in aqueous buffer (500 ml) containing N-methylmorpholine and acetic acid (pH about 7.0). The above biphasic reaction mass was hydrogenated for 3 hours under pressure at 20-25°C. After completion of the reaction, the mixture was filtered and aqueous layer was separated. The aqueous layer was extracted with ethyl acetate (300 ml). To the aqueous layer was added isopropyl alcohol (1.5 L) slowly at a temperature of about 0-5°C and the resultant mass was stirred for 3 hours at 0-5°C. The separated solids were filtered, washed with chilled acetone and dried at ambient temperature under vacuum to get meropenem trihydrate in a yield of 22.0 gm.

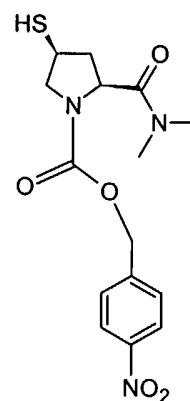
We claim:

1. A process for the preparation of meropenem comprising:

- a) reacting an enol-phosphate of Formula III with a thiopyrrolidine of Formula IV to make a compound of Formula V,

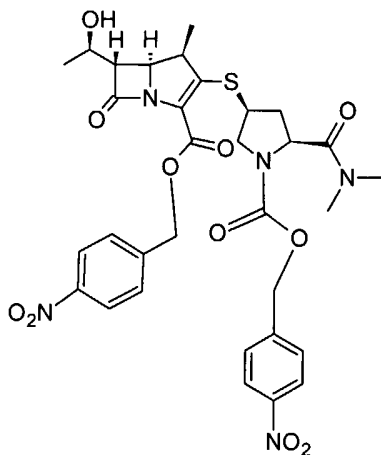


FORMULA II



FORMULA IV

- b) deprotecting the compound of Formula V by hydrogenolysis to make meropenem, and

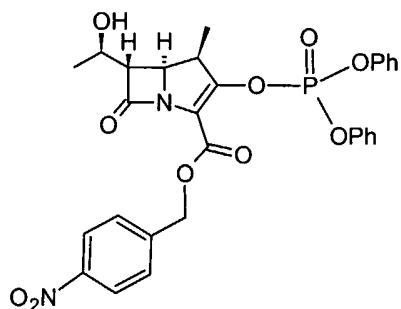
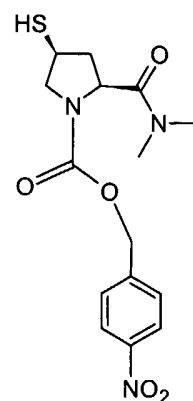


FORMULA V

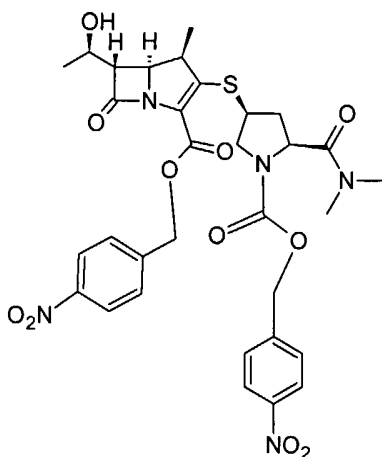
- c) isolating meropenem from the reaction mass thereof,
wherein the compound of Formula V is not isolated before deprotection.

2. A process for the preparation of meropenem comprising:

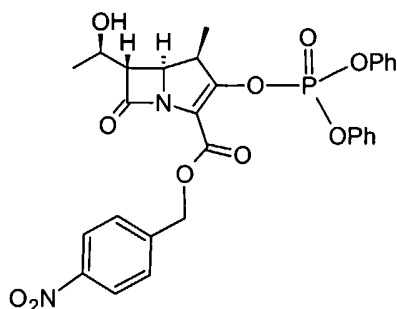
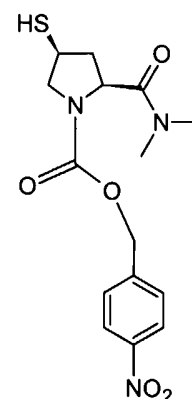
- a) reacting the enol-phosphate of Formula III with the thiopyrrolidine of Formula IV to make the compound of Formula V,

**FORMULA II****FORMULA IV**

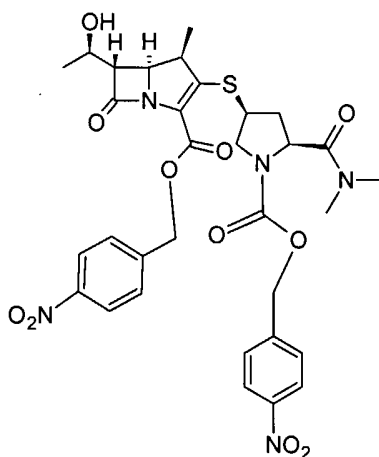
- b) deprotecting the compound of Formula V by hydrogenolysis to make meropenem wherein the deprotection is carried out in a biphasic system, and

**FORMULA V**

- c) isolating meropenem from the reaction mass thereof.
3. A process for the preparation of meropenem comprising:
- a) reacting the enol-phosphate of Formula III with thiopyrrolidine of Formula IV to make a compound of Formula V,

**FORMULA II****FORMULA IV**

- b) deprotecting the compound of Formula V by hydrogenolysis to make meropenem, wherein N-methylmorpholine and an acid are used as buffering agents, and

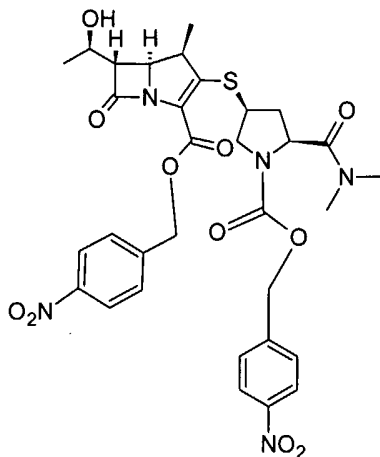
**FORMULA V**

- c) isolating meropenem from the reaction mass thereof.

4. A process as claimed in claims 1, 2 or 3, wherein step a) is carried out at a temperature of from about -60° to about -10°C .
5. A process as claimed in claims 1, 2 or 3, wherein step a) is carried out in the presence of a secondary amine.
6. A process as claimed in claim 5, wherein the secondary amine is diisopropylamine.
7. A process as claimed in claims 1, 2 or 3, wherein deprotection is carried out using palladium catalyst.
8. A process as claimed in claim 3, wherein the acid is acetic acid.

1 9. A process for the preparation of meropenem trihydrate comprising:

2 a) deprotecting a compound of Formula V by hydrogenolysis to make
3 meropenem in an aqueous layer,



FORMULA V

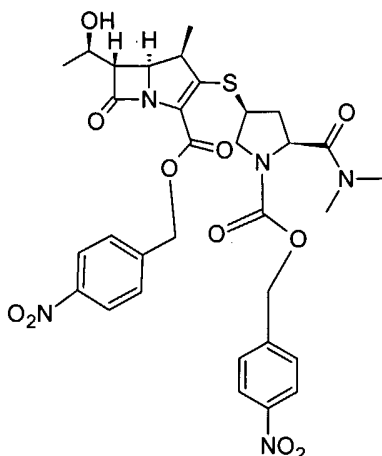
6 b) separating the aqueous layer containing meropenem from the reaction
7 mass,

8 c) adding a water-miscible organic solvent to the aqueous layer to precipitate
9 meropenem trihydrate from the aqueous solution, and

10 d) isolating pure meropenem trihydrate from the reaction mass thereof.

1 10. A meropenem trihydrate having purity greater than 98% prepared by a process
2 comprising:

a) deprotecting a compound of Formula V by hydrogenolysis to make meropenem in an aqueous layer,



FORMULA V

b) separating the aqueous layer containing meropenem from the reaction mass,

c) adding a water-miscible organic solvent to the aqueous layer to precipitate meropenem trihydrate from the aqueous solution, and

d) isolating meropenem trihydrate having purity greater than 98% from the reaction mass thereof.

11. A process as claimed in claims 9 or 10, wherein step a) is carried out in the presence of palladium catalyst.

12. A process as claimed in claims 9 or 10, wherein the water-miscible organic solvent is selected from a group consisting of acetone, tetrahydrofuran, and isopropanol.

13. A process as claimed in claims 9 or 10, wherein the water miscible-organic solvent is acetone.

14. A process as claimed in claims 9 or 10, wherein step c) is carried out at a temperature of from about -20° to about 25°C .

15. A process as claimed in claims 9 or 10, wherein step d) comprises filtration or centrifugation.