Title: A PROCESS FOR PREPARATION OF ERTAPENEM

Abstract: The present invention relates to a novel process for the preparation of 1-[N-[(R)-2-methyl-2-oxo-3-(2-oxo-2H-chromen-3-yl)propyl]carbamoyl]carbamate, Ertapenem of formula 1. The process comprises isolation of monoprotected Ertapenem salt and further deprotection to obtain Ertapenem monosodium.

Figure: X-Ray diffractogram of ertapenem monosodium

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
29 March 2012 (29.03.2012)

(51) International Patent Classification:
C07D 477/08 (2006.01)

(21) International Application Number:
PCT/IN2011/000656

(22) International Filing Date:
22 September 2011 (22.09.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2809/CHE/2010 24 September 2010 (24.09.2010) IN

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Declared under Rule 4.17:
- of inventorship (Rule 4.17(iv))

Published:
- without international search report and to be republished upon receipt of that report (Rule 48.2(g))
A Process for Preparation of Ertapenem

FIELD OF INVENTION

The present invention relates to a novel process for the preparation of 1β-methylcarbapenem antibiotic, Ertapenem of formula I.

BACKGROUND OF THE INVENTION

Ertapenem is a sterile, synthetic, parenteral, 1-β methyl-carbapenem that is structurally related to beta-lactam antibiotics. It is marketed by Merck as Invanz®. It is structurally very similar to Meropenem in that it possesses a 1-β methyl group. Ertapenem is used as antibiotic agent in the treatment of moderate to severe complicated foot infection due to indicated pathogens in diabetic patients without osteomyelitis, and also useful in the treatment of pneumonia, urinary tract infections, intra-abdominal, gynaecological, skin, and soft tissue infections, meningitis, septicaemia and febrile Neutrogena.

A number of synthetic processes are reported for the preparation of Ertapenem. US patent 5,478,820 describes a process for preparation of Ertapenem where it is isolated by using column purification as well as freeze-drying technique. This patent also describes a process of preparation of disodium salt of Ertapenem by dissolving crude product in water using NaHCO₃, followed by purification using column chromatography and subsequent lyophilisation.

US patent No. 6,504,027 provides a process for preparing Ertapenem in crystalline form which comprises deprotecting and extracting a polar organic solution containing a crude monoprotected Ertapenem disodium salt with C₄₋₁₀ alcohol in the presence of ion-pairing reagent followed by adjusting the pH to 5.5, collecting and crystallizing the resultant aqueous phase to produce Ertapenem disodium. This process involves a number of operations like extraction, it is not preferred at industrial scale.

These processes are not attractive for industrial scale production because they involve chromatographic purification in certain stages for purification.
The present inventors has developed a process which is more practical, efficient, cost effective and which removes lot of impurity to yield a highly pure product without doing column chromatographic purification.

**SUMMARY OF THE INVENTION**

Accordingly, the main aspect of the present invention is to provide a process for preparation Ertapenem monosodium comprising:

a) condensing the compound of formula II with compound of formula III in presence of a base and a solvent to obtain a monoprotected compound of formula IV or its sodium salt;

b) optionally isolating monoprotected compound of formula IV or its sodium salt;

c) deprotecting the monoprotected compound of formula IV or its sodium salt in a solvent in presence or absence of a buffer and in presence or absence of a sodium ion source; and

d) extracting the product with optional pH adjustment to obtain Ertapenem of formula I or its monosodium salt.

The above process is illustrated in below scheme:
The another aspect of the present invention is to provide a novel crystalline form of Ertapenem monosodium characterised by having X-ray powder diffraction pattern as given in figure 1 and having a 2θ peaks at 4.1, 7.14, 9.62, 12.3, 20.43, 22.43, 29.03, 30.65 and 31.8±0.2.

The another aspect of the present invention is to provide a novel amorphous form of monoprotected ertapenem acid characterized by X-ray powder diffraction pattern as given in figure 2.

The another aspect of the present invention is to provide a novel amorphous form of monoprotected ertapenem monosodium characterized by X-ray powder diffraction pattern as given in figure 3.

**Brief Description of the Diagram/Figure**

Figure 1: X-Ray diffractogram of Ertapenem monosodium of the present invention

Figure 2: X-Ray diffractogram of monoprotected ertapenem acid of the present invention

Figure 3: X-Ray diffractogram of monoprotected ertapenem monosodium of the present invention

**DETAIL DESCRIPTION OF THE INVENTION**

In an embodiment of the present invention, the protective group P selected from group such as allyl, 2,2,2-trichloroethyl, 2-bromoethyl, benzhydryl, trityl, aryl, trimethylsilyl, triethylsilyl, 4-methoxybenzyl, t-butyl, p-nitrobenzyl and the like, preferably P and P" is selected from P-nitrobenzyl.

In another embodiment of the present invention, the solvent used in step (a) is selected from the group consisting of diethyl ether, tetrahydrofuran, toluene, xylene, dichloromethane, 1,2-dichloroethane, N,N-dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, N-ethylpyrrolidinone, N-methylpiperidinone, acetonitrile, propionitrile, and mixtures thereof, preferably N,N-dimethylformamide; and inorganic base used is selected from diisopropylethylamine (DIPEA), diisopropylamine (DIPA), dicyclohexylamine (DCHA), 2,2,6,6-tetramethylpiperidine (TMP), 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU) 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpyrrolidine, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, disodium hydrogen phosphate, and the like preferably 1,8-
diazabicyclo[4.3.0.]undec-7-ene (DBU). The condensation reaction may optionally contain bases like N,N-dimethylaminopyridine, N,N-diethylamino pyridine to avoid impurity formation.

In another embodiment of the present invention the monoprotected compound of formula (IV) can be isolated as an acid or a sodium salt, using mixture of ethyl acetate, alcohol and isopropyl ether. The monoprotected acid or its sodium salt was subjected to de-protection to yield Ertapenem monosodium. The sodium salt of formula (IV) is more stable, and easy to handle in industrial point of view.

In another embodiment, monoprotected compound of formula (IV) or its sodium salt is optionally isolated by quenching the reaction mass from step (i) into a buffer solution selected from dipotassium hydrogen orthophosphate, or potassium dihydrogen orthophosphate, or water and the like followed by extracting the compound in an organic solvent like ethyl acetate, MDC (dichloromethane) preferably in MDC and precipitating the compound of formula (IV) directly from the resultant organic layer or by quenching the organic layer into a solvent selected from hexane, heptane, IPE (diisopropylether), methyl tert-butyl ether and the like or mixtures thereof. The intermediate of formula (IV) can be taken to next stage with or without isolation. Alternatively the intermediate of formula (IV) can be directly precipitated from the buffer solution or water.

In yet another embodiment of the present invention, the deprotection is preferably done by hydrogenolysis. The hydrogenolysis is usually done in presence of a metal catalyst, preferably in presence of hydrogen gas and palladium (Pd/C) catalyst. The solvent for deprotection in step (c) is selected from THF, acetonitrile, dioxane, ethyl acetate, isopropyl alcohol, n-propanol, methanol, dichloromethane, DMF, MDC, aqueous carbonic acid, water or mixtures thereof preferably aqueous MDC and n-propanol. The de-protection of protecting groups can be carried out using a mixture of solvents either in single phase or in biphasic medium. If required, the hydrogenation process can employ employs sodium ion source base such as sodium bicarbonate, sodium hydroxide, and sodium carbonate.

In yet another embodiment of the present invention, after completion of hydrogenation, the product was taken into aqueous medium, followed by optionally washing with organic solvents like MDC, butyl acetate, ethyl acetate, toluene, hexane, 1,2-dibromoethane and the like to remove reaction by-products and/or impurities. After hydrogenation, optionally carbon dioxide gas was purged to the reaction mass. The aqueous layer was subjected to degassing technique to remove the dissolved solvent if required. Further depending on the requirement, pH of aqueous layer optionally was adjusted using acid like acetic acid, formic acid, HCl, etc to obtain the compound of formula (I).
In yet another embodiment of the present invention, the pH of aqueous layer containing the Ertapenem monosodium was optionally reduced to 5 followed by quenching in to an alcohol yielding the compound of formula (I) as monosodium.

In yet another embodiment of the invention the crystalline form of Ertapenem monosodium is novel and it is characterised by X-ray powder diffraction pattern same as given in figure 1 and having 20 peaks at 4.1, 7.14, 9.62, 12.3, 20.43, 22.43, 29.03, 30.65 and 31.8±0.2. This novel crystalline form of Ertapenem is very stable and the form doesn’t change with time for a considerably long time.

In yet another embodiment of the invention the crystalline form of Ertapenem monosodium is characterised by having further X-ray powder diffraction 2θ peaks at 4.30, 5.09, 7.97, 10.77, 14.26, 15.03, 17.01 18.96, 25.94, 26.48, 27.41, 28.47, 29.87, 32.24, 32.67, 33.09, 33.36, 33.90, 35.41, 36.22, 37.72, 39.83, 42.72, 43.14, 44.67, 46.24 and 49.21±0.2.

In yet another embodiment of the invention the monoprotected ertapenem acid and monoprotected ertapenem monosodium are amorphous in nature as shown in figure 2 and figure 3 respectively.

In still further embodiment of the present invention, the starting material compound of formula (III) is prepared by utilizing technique known in the art.

Advantage of the process of the present invention:

a) The use of monoprotected intermediate of Ertapenem gives higher yield 0.5w/w to 0.6w/w as compared to 0.2w/w to 0.3w/w obtained in prior art.

b) Hydrogenation using MDC gives faster layer separation & adds to the yield.

c) The present process avoids hydrogenation work up as described in innovator patent.

d) The present process avoids purification of final compound to obtain a purity of more than 98% whereas the prior art processes need a purification to achieve this purity.

e) Avoid consumption of more palladium carbon

The present invention is illustrated with the following non-limiting examples.

Example 1:

Step-I: Preparation of monoprotected Ertapenem monosodium

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(diphenoxyphosphinyl)oxy]-6-(1-hydroxyethyl)-4-methyl-7-oxo-(4-nitrophenyl)methyl ester, [4R-[4a,5b,6b(R*)]] (MAP) (25 g) and
Ertapenem side chain -[(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido]benzoic acid hydrochloride were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU was added at the same temperature. After completion of the reaction, the reaction mass was quenched into buffer solution (KH₂PO₄ in water). The pH was adjusted by using phosphoric acid. The product has been extracted with adding MDC and washed with water. Sodium-2-ethyl Hexanoate was dissolved in methanol and was added into the organic layer. This mixture was quenched in to IPE and precipitated solid was filtered and washed, dried to obtain monoprotected Ertapenem monosodium.

Yield -32g; purity:98%

**Step-II: Preparation of Ertapenem mono sodium NS**

The monoprotected ertapenem monosodium (25 g) obtained above was dissolved in MDC and n-propanol at 0°C to 5°C and DM water was added to it. Pd/c was slurryfied in DM H₂O and added to it, stirred under H₂ atm at 3°C to 5°C. After the reaction completion Pd/c was filtered and washed with DM H₂O. Organic layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aqueous layer at -3°C to -5°C and then cooled to -20°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol. Crystals were filtered off and washed by using chilled Ethanol at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

YIELD 12.5 g; purity: 98%; M/C: 10 to 16%

**Step-III : Preparation of Ertapenem Sterile**

Ertapenem monosodium (NS) 50gm was dissolved in water-for-injection(WFI) water in presence of sodium bicarbonate & sodium hydroxide at 2-5°C. The clear filtrate was filtered through 0.2micron and it vial lyophilized.

Yield =50 g; purity: 97%

**Example 2:**

**Step-I: Preparation of monoprotected Ertapenem monosodium**

MAP (25 g) and Ertapenem side chain -[(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido] benzoic acid hydrochloride were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU was added at the same temperature. After completion of the reaction, the reaction mass was quenched into buffer solution (KH₂P0₄ in water). The pH was adjusted by using phosphoric acid. The product was extracted with adding MDC and washed with water. The pH of MDC layer
was adjusted to 7.0 -8.0 in presence of water by using Sodium bicarbonate and directly taken for next step.

**Step-II: Preparation of Ertapenem mono sodium NS**

Monoprotected Ertapenem monosodium was stirred in water, MDC and n-propanol at 0°C - 5°C. Pd/c slurryfied in DM H₂O was added to it and stirred under H₂ atm at 3°C-5°C. After the completion of reaction Pd/c was filtered and washed with DM water, organic layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aq layer at -3°C to -5°C and then cooled to -20°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol. Crystals were filtered off and washed by using chilled Ethanol at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

YIELD = 13.3 g; Purity=98%; M/C: 10 to 16%

**Example 3:**

**Step-I: Preparation of monoprotected Ertapenem acid**

MAP (25 g) and Ertapenem side chain -(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido] benzoic acid hydrochloride (16 g) were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU was added at the same temperature. After completion of reaction, the reaction mass was quenched into buffer solution (KH₂PO₄ in water). The pH was adjusted by using phosphoric acid. The product was extracted with adding MDC and washed with water. This layer directly taken for next stage.

**Step-II: Preparation of Ertapenem mono sodium NS**

The above MDC layer of Monoprotected Ertapenem acid was dissolved in n-propanol at 0°C -5°C and sodium bicarbonate and DM water were added to it. Pd/C was slurryfied in DM H₂O and added, stirred under H₂ atmosphere at 3°C-5°C, after the reaction completion Pd/C was filtered and washed with DM H₂O. The MDC layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aq layer at -3°C to -5°C and then cooled to -20°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol. Crystals were filtered off and washed by using chilled Ethanol at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

YIELD = 13.3 g; Purity=98% ; M/C: 10 to 16%
Example 4:

**Step-I: Preparation of monoprotected Ertapenem acid**

MAP (25 g) and Ertapenem side chain \[(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido\]benzoic acid hydrochloride were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU was added at the same temperature. After completion of reaction, reaction mass was quenched into Buffer solution (KH2PO4 in water). The pH was adjusted by using phosphoric acid. The product was extracted by adding MDC and washed with water. The MDC layer was added with methanol and methyl tertiarybutyl ether and precipitated the monoprotected ertapenem acid. The precipitated solid was filtered, washed and dried.

Yield: 30g; Purity=98%

**Step-II: Preparation of Ertapenem mono sodium NS**

Monoprotected ertapenem acid (25g) was dissolved in MDC and n-propanol at 0°C to 5°C. Sodium bicarbonate and DM H2O were added to it at the same temperature. Pd/c was slurried in DM H2O and was added to above mass, stirred under H2 atmosphere at 3°C to 5°C. After the completion of reaction Pd/c was filtered and washed with DM H2O. MDC layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aqueous layer at -3°C to -5°C and then cooled to -20°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol. Crystals were filtered off and washed by using chilled Ethanol at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

Yield: 12.5 g; Purity=98%; M/C: 10 to 16%

Example 5:

**Step-I: Preparation of monoprotected Ertapenem monosodium**

MAP (25 g) and Ertapenem side chain \[(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido\]benzoic acid hydrochloride were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU in-50ml-DMF was added at the same temperature. After completion of the reaction, the reaction mass was quenched into buffer solution (KH2PO4 in water). The pH was adjusted by using phosphoric acid. The product was extracted with adding MDC and washed with water. The pH of MDC layer was adjusted to 7.0 -8.0 in presence of water by using Sodium bicarbonate and directly taken for next step.

**Step-II: Preparation of Ertapenem mono sodium NS**
Monoprotected Ertapenem monosodium was stirred in water, MDC and n-propanol at 0°C - 5°C. Pd/c slurried in DM H₂O was added to it and stirred under H₂ atm at 3°C-5°C. After the completion of reaction Pd/c was filtered and washed with DM water, organic layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed with EDTA, Sodium dithionite and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aq layer cooled to 30°C to -50°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol at -20°C. Crystals were filtered off and washed by using chilled aqueous Ethanol at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

**YIELD = 13.5 g ; Purity=98%; M/C: 10 to 16%**

**Example 6:**

**Step-I: Preparation of monoprotected Ertapenem monosodium**

MAP (25 g) and Ertapenem side chain -[(2S,4S)-4-Mercaptopyrrolidine-2-carboxamido] benzoic acid hydrochloride were dissolved in DMF at RT. Reaction mass was cooled to -50°C to -60°C. DBU was added at the same temperature. After completion of the reaction, the reaction mass was quenched into buffer solution (KH₂PO₄ in water). The pH was adjusted by using phosphoric acid. The product was extracted with adding MDC and washed with water .The pH of MDC layer was adjusted to 7.0 -8.0 in presence of water by using Sodium bicarbonate and directly taken for next step.

**Step-II: Preparation of Ertapenem mono sodium NS**

Monoprotected Ertapenem monosodium was stirred in water, MDC and n-propanol at 0°C - 5°C. Pd/c slurried in DM H₂O was added to it and stirred under H₂ atm at 3°C-5°C. After the completion of reaction Pd/c was filtered and washed with DM water, organic layer was separated. The aqueous layer was washed with MDC, treated with Carbon at 0°C -5°C, degaussed with EDTA, Sodium dithionite and filtered. It was re-filtered through 0.2 µ filter paper and methanol was added into the aq layer cooled to 3°C to -5°C. The pH was adjusted with acetic acid in methanol to 4.5-5.0 and crystallized by adding n-propanol at -20°C. Crystals were filtered off and washed by using chilled Acetone at -3°C to -5°C, filtered solid was dried under Vacuum and nitrogen.

**YIELD = 13.5 g ; Purity=98%; M/C: 10 to 16%**
We claim:

1. A process for preparation Ertapenem monosodium of formula I comprising:

   a) condensing the compound of formula II with compound of formula III in presence of a base and a solvent to obtain a monoprotected compound of formula IV or its sodium salt;

   Where \( P \) is a protecting group

   b) optionally isolating monoprotected compound of formula IV or its sodium salt;

   c) deprotecting the monoprotected compound of formula IV or its sodium salt in a solvent in presence or absence of a buffer and in presence or absence of a sodium ion source; and
d) extracting the product with optional pH adjustment to obtain Ertapenem of formula I or its monosodium salt.

2. A process for preparation of ertapenem monosodium according to claim 1 wherein, the solvent for the deprotection in step (c) is selected from THF, acetonitrile, dioxane, ethyl acetate, isopropyl alcohol, n-propanol, methanol, dichloromethane, DMF, MDC, aqueous carbonic acid, water or mixtures thereof preferably aqueous MDC and n-propanol.

3. A process for preparation of ertapenem monosodium according to claim 1 wherein, the deprotection is carried out in presence of a metal catalyst preferably Pd/C.

4. A process for preparation of ertapenem monosodium according to claim 1 wherein, the solvent for condensation in step (a) is selected from the group consisting of diethyl ether, tetrahydrofuran, toluene, xylene, dichloromethane, 1,2-dichloroethane, N,N-dimethylformamide, dimethylacetamide, N-methylpyrrolidinone, N-ethylpyrrolidinone, N-methylpiperidinone, acetonitrile, propionitrile, and mixtures thereof, preferably N,N-dimethylformamide;

5. A process for preparation of ertapenem monosodium according to claim 1 wherein, the base for condensation in step (a) is selected from the group consisting of diisopropylethylamine (DIPEA), diisopropylamine (DIPA), dicyclohexylamine (DCHA), 2,2,6,6-tetramethylpiperidine (TMP), 1,1,3,3-tetramethylguanidine (TMG), 1,8-diazabicyclo[4.3.0.]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), N-methylpyrrolidinone, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, disodium hydrogen phosphate, and the like preferably 1,8-diazabicyclo[4.3.0.]undec-7-ene (DBU).

6. A process for preparation of ertapenem monosodium according to claim 1 wherein, the pH adjustment in step (d) is carried out using acetic acid in methanol.

7. A crystalline form of Ertapenem monosodium characterised by X-ray powder diffraction pattern same as given in figure 1 and having 2θ peaks at 4.1, 7.14, 9.62, 12.3, 20.43, 22.43, 29.03, 30.65 and 31.8±0.2.

8. An amorphous form of monoprotected ertapenem acid.

Figure: X-Ray diffractogram of ertapenem monosodium
Figure 2: X-Ray diffractogram of monoprotected ertapenem acid
Figure 2: X-Ray diffractogram of monoprotected ertapenem monosodium