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

(57) Abstract: The present invention is related to processes for the preparation of faropenem.

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Description

A PROCESS FOR THE PREPARATION OF FAROPENEM

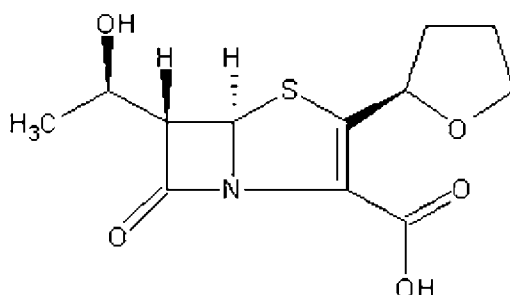
[1] Field of the Invention

[2] The present invention is related to processes for the preparation of faropenem.

[3] Background of the Invention

[4] (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2R)-tetrahydrofuran-2-yl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, commonly known as faropenem of Formula I is a synthetic, broad-spectrum, carbapenem antibiotic.

[5]



[6] **FORMULA I**

[7] The sodium salt of faropenem shows potent antibacterial activity against methicillin-sensitive *Staphylococcus aureus* (MSSA), *Streptococcus pyogenes* and *Streptococcus pneumoniae* and gram-positive bacteria such as penicillin-resistant pneumococci (PRSP), oral *staphylococci* and *enterococci*. It also shows a wide antibacterial spectrum covering gram-negative bacteria such as *Haemophilus influenzae* and anaerobic bacteria such as the genus *Bacteroides*.

[8] U.S. Patent No 4,997,829 provides a process for the preparation of sodium and potassium salts of faropenem, involving the deprotection of allyl faropenem in the presence of triphenylphosphine, palladium tetrakis-triphenylphosphine and sodium or potassium 2-ethylhexanoate. However, the process disclosed in the '829 patent does not result in stable and commercially useful hydrates of faropenem salts.

[9] EP Patent No. 410,727 provides various processes for preparing the hemipentahydrate of faropenem salts, involving the deprotection of allyl faropenem in the presence of an alkali metal enolate of 1,3-diketone. The faropenem formed in situ is converted into hemipentahydrate by the addition water. JP Patent No 2,949,363 B2 also provides a process for preparing hydrates of faropenem salts by treating deprotected faropenem with an alkali metal salt of a C₁₄ carboxylic acid in the presence of water.

[10] The water added to the reaction mixture to effect the formation of hydrates in the prior art processes is removed by distillation. However, the removal of water from the reaction mixture under reduced pressure consumes both time and energy. Additionally

the solution stability of faropenem sodium in water is very poor and prolonged storage or heating results in impurity formation.

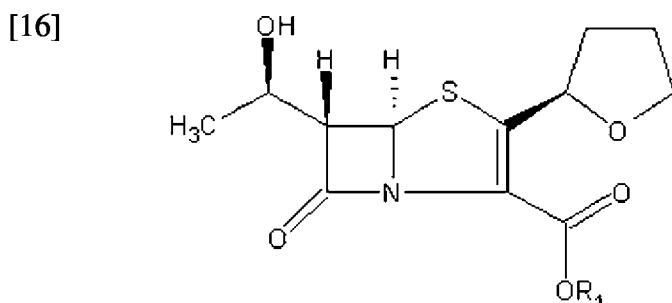
[H] Summary of the Invention

[12] While working on this problem, the present inventors have developed advantageous processes for the preparation of hydrates of alkali metal salts of faropenem. The present process does not involve the removal of water and it provides the hydrates of faropenem with higher yield, reduced time cycle and greater purity, rendering the process economical and industrially viable.

[13] Detailed Description of the Invention

[14] In one aspect, a process for the preparation of a hydrate of an alkali metal salt of faropenem is provided, wherein the process comprises,

[15] a) treating the compound of Formula π ,



[17] FORMULA II

[18] wherein R_1 is selected from optionally substituted C_1-C_8 alkyl, optionally substituted C_3-C_8 alkenyl, optionally substituted C_7-C_{19} aralkyl, or optionally substituted C_6-C_{12} aryl,

[19] with an alkali metal salt of a substituted or unsubstituted C_{5-10} carboxylic acid and catalytic amount of a palladium complex in the presence of an organic solvent;

[20] b) treating the reaction mixture of step a) with water and a water-miscible solvent; and

[21] c) isolating a hydrate of an alkali metal salt of faropenem from the reaction mass thereof,

[22] wherein water is not removed from the reaction mixture in step b) or c).

[23] The compound of Formula II can be prepared, for example, according to methods provided in the prior art mentioned above. The compound of Formula II can be dissolved in an organic solvent, selected from, for example, dichloromethane, dichloroethane, chloroform, methyl acetate, ethyl acetate, tetrahydrofuran, diethyl ether, methanol, ethanol, acetonitrile, propionitrile, acetone or methyl ethyl ketone. The solution so obtained can be treated with an alkali metal salt of a substituted or unsubstituted C_{5-10} carboxylic acid and catalytic amount of a palladium complex. The C_{5-10} carboxylic acid can be 2-ethylhexanoic acid, pentanoic acid, hexanoic acid or

heptanoic acid. The acid can be used in the form of an alkali metal salt or an alkali metal hydroxide together with C₅₋₁₀ carboxylic acid can be used. The palladium complex can be selected from, for example, tetrakis(triphenylphosphine) palladium (0), bis(triphenylphosphine) palladium (II) dichloride, dichloro-di-(benzonitrile palladium (II), or palladium diacetate. The palladium complex can be used together with a phosphine ligand such as triarylphosphine.

[24] Addition of water to the reaction mixture helps in the formation of the hydrates of faropenem salt. Addition of a water-miscible solvent to the reaction mixture facilitates the precipitation of the hydrate. The water-miscible solvent can be selected from, for example, acetone, tetrahydrofuran, methanol, ethanol, isopropyl alcohol, dioxane or acetonitrile. The hydrate of alkali metal salt of faropenem can be isolated from the reaction mixture by filtration.

[25] 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 intended to be included within the scope of the present invention.

[26] Example 1 Preparation of Faropenem Sodium Hemipentahydrate:

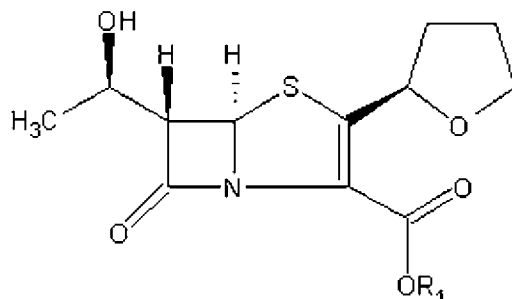
[27] Allyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2R)-tetrahydrofuran-2-yl] - 4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (72 g, 0.221 mol) was dissolved in methylene chloride (950 ml). The solution was cooled to 10°C and triphenyl phosphine (2.0 g, 0.0076 mol), sodium-2-ethylhexanoate (39.71 g, 0.239 mol) and tetrakis triphenylphosphine palladium (0) (2.0 g) were added together at 10°C. The reaction mixture was stirred for 1-2 hours at 10-15°C. After the completion of reaction, water (50 ml) was added to the reaction mixture. The reaction mixture was stirred for 15 minutes, followed by the addition of acetone (332.5ml) and the reaction mixture was cooled to 0°C. The solid so separated from the reaction mixture was filtered, washed with acetone and dried under reduced pressure to obtain the title compound.

[28] Yield: 64 g; Purity by HPLC: 99.0%.

Claims

- [1] A process for the preparation of a hydrate of an alkali metal salt of faropenem, wherein the process comprises,

a) treating the compound of Formula II,



FORMULA π

wherein R_1 is selected from a group comprising of optionally substituted C_1 - C_8 alkyl, optionally substituted C_3 - C_8 alkenyl, optionally substituted C_7 - C_{19} aralkyl, or optionally substituted C_6 - C_{12} aryl, with an alkali metal salt of a substituted or unsubstituted C_{5-10} carboxylic acid and a catalytic amount of a palladium complex in the presence of an organic solvent;

b) treating the reaction mixture of step a) with water and a water miscible solvent,

c) isolating a hydrate of an alkali metal salt of faropenem from the reaction mass thereof,

wherein water is not removed from the reaction mixture in step b) or c).

- [2] The process as claimed in claim 1, wherein the hydrate of an alkali metal salt of faropenem is faropenem sodium hemipentahydrate.
- [3] The process as claimed in claim 1, wherein the C_{5-10} carboxylic acid is 2-ethylhexanoic acid.
- [4] The process as claimed in claim 1, wherein the palladium complex is selected from tetrakis(triphenylphosphine) palladium (O), bis(triphenylphosphine) palladium (II) dichloride, dichloro-di-(benzonitrile palladium (II)), or palladium diacetate.
- [5] The process as claimed in claim 4, wherein the palladium complex is tetrakis(triphenylphosphine) palladium (O).
- [6] The process as claimed in claim 1, wherein the organic solvent is selected from dichloromethane, dichloroethane, chloroform, methyl acetate, ethyl acetate, tetrahydrofuran, diethyl ether, methanol, ethanol, acetonitrile, propionitrile, acetone or methyl ethyl ketone.

- [7] The process as claimed in claim 1, wherein the palladium complex is used along with a phosphine ligand.
- [8] The process as claimed in claim 7, wherein the phosphine ligand is triaryl phosphine.
- [9] The process as claimed in claim 1, wherein the water-miscible solvent is selected from acetone, tetrahydrofuran, methanol, ethanol, isopropyl alcohol, dioxane or acetonitrile.
- [10] The process as claimed in claim 9, wherein the water-miscible solvent is acetone.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/053651

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D499/88

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)
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 , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	EP 0 410 727 A (SUNTORY LTD [JP]) 30 January 1991 (1991-01-30) cited in the application example 1	1-10
Y	EP 0 199 446 A1 (SUNTORY LTD [JP]) 29 October 1986 (1986-10-29) cited in the application examples 38,39,42,43,45,46	1-10

D Further documents are listed in the continuation of Box C

☒ See patent family annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/053651

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