(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199746076 B2
(10) Patent No. 714155

(54) Title
Process for synthesizing carbapenem side chain intermediates

(51)[6] International Patent Classification(s)
C07F 009/22 C07F 009/572

(21) Application No: 199746076 (22) Application Date: 1997 .10 .06

(87) WIPO No: WO98/15561

(30) Priority Data

(31) Number	(32) Date	(33) Country
60028966	1996 .10 .10	US
9700696	1997 .01 .15	GB

(43) Publication Date : 1998 .05 .05
(43) Publication Journal Date : 1998 .06 .25
(44) Accepted Journal Date : 1999 .12 .23

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OPI DATE 05/05/98 APPLN. ID 46076/97
AOJP DATE 25/06/98 PCT NUMBER PCT/US97/17955
AU9746076

IN

(51) International Patent Classification 6 : C07F 9/22, 9/572

A1

(11) International Publication Number: WO 98/15561

(43) International Publication Date: 16 April 1998 (16.04.98)

(21) International Application Number: PCT/US97/17955

(22) International Filing Date: 6 October 1997 (06.10.97)

(30) Priority Data:

60/028,966	10 October 1996 (10.10.96)	US
9700696.9	15 January 1997 (15.01.97)	GB

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

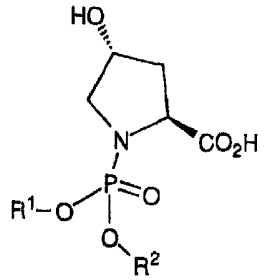
Published

With international search report.

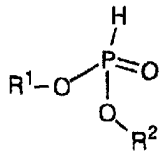
(54) Title: PROCESS FOR SYNTHESIZING CARBAPENEM SIDE CHAIN INTERMEDIATES

(57) Abstract

A process for the synthesis of an N-(di-substituted phosphoryl)-trans-4-hydroxy-L-proline of formula (I) is disclosed, wherein R^1 and R^2 independently represent C_{1-18} alkyl, phenyl or phenyl-substituted C_{1-18} alkyl, or R^1 and R^2 are taken in combination to represent C_{2-4} alkylidene or phenyl. Trans-4-hydroxy-L-proline is reacted with a di-(substituted) phosphite of formula (III) in the presence of sodium hypochlorite and sodium hydroxide to produce a compound of formula (I).



(I)



(III)

TITLE OF THE INVENTION

PROCESS FOR SYNTHESIZING CARBAPENEM SIDE CHAIN INTERMEDIATES

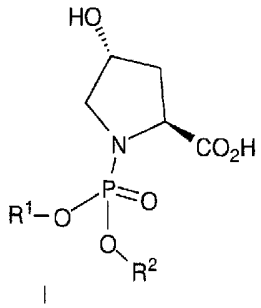
BACKGROUND OF THE INVENTION

The present invention relates to a process of synthesizing compounds that are useful in the manufacture of carbapenem side chains. These carbapenem antibiotic compounds are effective in the treatment of infections caused by susceptible bacterial organisms.

In the past, the synthesis of appropriately substituted hydroxyprolines has been conducted in the presence of a mixture of carbon tetrachloride, an amine base, e. g., triethylamine, water and an inert organic cosolvent, e.g., ethanol. See, e.g., Synthesis, 1988: 444-448. This process is somewhat undesirable in that it uses excess amounts of reagents and it uses and generates chlorinated hydrocarbons. The present invention utilizes stoichiometric amounts of more economical reagents and generates little undesirable side products.

SUMMARY OF THE INVENTION

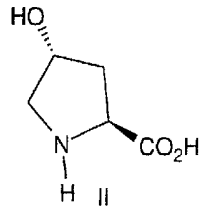
A process for the synthesis of an N-(di-substituted phosphoryl)-trans-4-hydroxy-L-proline of the formula I :



I

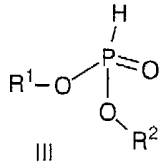
wherein R^1 and R^2 independently represent C_{1-18} alkyl, phenyl or phenyl-C_{1-18} alkyl, or R^1 and R^2 are taken in combination to represent C_{2-4} alkylidene or phenyl,

is disclosed wherein trans-4-hydroxy-L-proline of the formula II:



II

is reacted with a di-(substituted) phosphite of the formula III:



III

in the presence of sodium hypochlorite and sodium hydroxide to produce a compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, C_{1-18} alkyl refers to straight and branched alkyl groups, including C_{5-18} alkyl groups which can be cyclic or bicyclic.

Likewise, the values of R^1 and R^2 include phenyl, phenyl-substituted C_{1-18} alkyl and C_{2-4} alkylidene. Preferred values of R^1 and R^2 include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, phenyl, benzyl, 2-ethylhexyl, decyl, lauryl and octadecyl. The preferred value of R^1 and R^2 taken in combination is ethylene or phenyl. The most preferred value of R^1 and R^2 is isopropyl.

The resulting compounds, III are useful in the synthesis of carbapenem antibiotics, such as the compounds that are described in U. S. Pat. No. 5,478,820 granted on December 26, 1995, and incorporated herein by reference.

Generally, the reaction ingredients are combined slowly at

a reduced temperature, e.g., about 0 to about 5°C. The pH can be maintained at about 9.0 by adding a suitable quantity of sodium hydroxide. In a preferred aspect of the invention, the pH of the reaction is maintained at about 9.0.

Sodium hypochlorite can be used in concentrations ranging from about 5% to about 20 weight %.

Upon completion of the reaction, the pH of the solution can be adjusted with acid, and the desired compound isolated. Typically a crystalline product can be obtained.

In a preferred embodiment of the invention, the process is as described above wherein R^1 and R^2 independently or in combination represent members selected from the group consisting of: methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, phenyl, benzyl, 2-ethylhexyl, decyl, lauryl, octadecyl and ethylene.

In a preferred embodiment of the invention, the present process is as described above wherein R^1 and R^2 independently represent C_{1-18} alkyl.

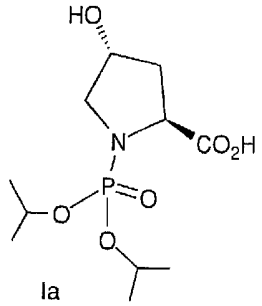
In another preferred embodiment of the invention, the process is as described above wherein R^1 and R^2 independently represent phenyl-substituted C_{1-18} alkyl.

In another preferred embodiment of the invention, the process is as described above wherein R^1 and R^2 represent phenyl.

In another preferred embodiment of the invention, the process is as described above wherein R^1 and R^2 taken in combination represent C_{2-4} alkylidene or phenyl.

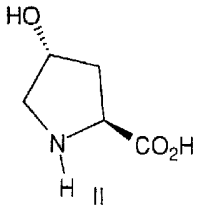
In another preferred embodiment of the invention, the process is as described above wherein R^1 and R^2 taken in combination represent ethylene or phenyl.

In a more preferred embodiment of the invention, the process described herein relates to the synthesis of N-(diisopropyl phosphoryl)-trans-4-hydroxy-L-proline of the formula Ia:



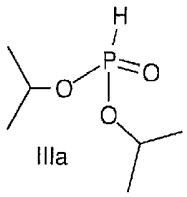
Ia

which comprises reacting trans-4-hydroxy-L-proline of the formula II:



II

with diisopropyl phosphite of the formula IIIa:

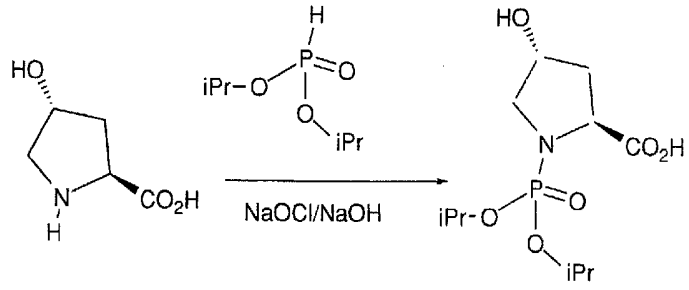


IIIa

in the presence of sodium hypochlorite and sodium hydroxide to produce a compound of formula Ia.

The invention is further illustrated with the following non-limiting example.

EXAMPLE 1



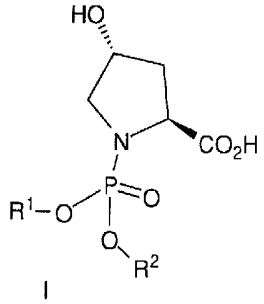
A mixture of water (12 L) and trans-hydroxy proline (5 Kg) was cooled to 0-5°C. The pH of the solution was adjusted to 9.0 with NaOH (25%) and diisopropylphosphite (7.0 kg) was added.

Sodium hypochlorite (12.5 wt % NaOCl) (20 L) was added while maintaining the pH at 9.0 by the addition of sodium hydroxide.

After completion, the reaction was quenched with sodium bisulfite (750 g.) over 15 minutes. The pH of the solution was adjusted from neutrality to approximately 2 by the addition of conc. HCl at 0-5°C, and sodium chloride (6.0 Kg) was added. The aqueous solution was extracted with isopropyl acetate (50 L aliquots at 0-5°C). The target compound (8.5 Kg) was isolated via crystallization.

WHAT IS CLAIMED IS:

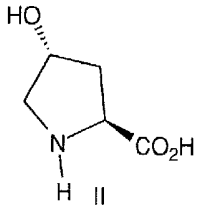
1. A process for the synthesis of an N-(di-substituted phosphoryl)-trans-4-hydroxy-L-proline of the formula I :



I

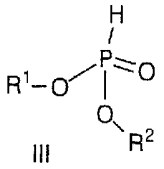
wherein R^1 and R^2 independently represent C_{1-18} alkyl, phenyl or phenyl-C_{1-18} alkyl, or R^1 and R^2 are taken in combination to represent C_{2-4} alkylidene or phenyl,

wherein trans-4-hydroxy-L-proline of the formula II:



II

is reacted with a di-(substituted) phosphite of the formula III:



III

in the presence of sodium hypochlorite and sodium hydroxide to produce a compound of formula I.

2. A process in accordance with claim 1 wherein R^1 and R^2 independently represent C_{1-18} alkyl.

3. A process in accordance with claim 1 wherein R^1 and R^2 independently represent phenyl-substituted C_{1-18} alkyl.

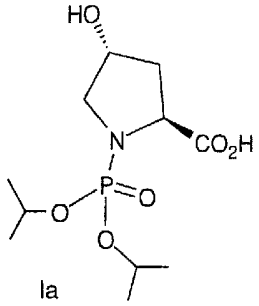
4. A process in accordance with claim 1 wherein R^1 and R^2 each independently represent phenyl.

5. A process in accordance with claim 1 wherein R^1 and R^2 taken in combination represent C_{2-4} alkylidene or phenyl.

6. A process in accordance with claim 5 wherein R^1 and R^2 taken in combination represent ethylene.

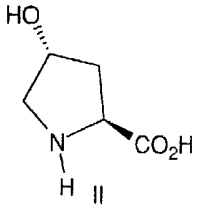
7. A process in accordance with claim 1 wherein R^1 and R^2 independently or in combination represent members selected from the group consisting of: methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, phenyl, benzyl, 2-ethylhexyl, decyl, lauryl, octadecyl and ethylene.

8. A process for the synthesis of N-(diisopropyl phosphoryl)-trans-4-hydroxy-L-proline of the formula Ia:



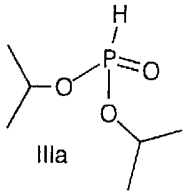
Ia

which comprises reacting trans-4-hydroxy-L-proline of the formula II:



II

with diisopropyl phosphite of the formula IIIa:



IIIa

in the presence of sodium hypochlorite and sodium hydroxide to produce a compound of formula Ia.

9. A process in accordance with claim 1 wherein the pH of the reaction is maintained at about 9.0.

10. A process for the synthesis of an N-(di-substituted phosphoryl)-trans-4-hydroxy-L-proline, substantially as hereinbefore described with reference to any one of the examples.

11. A process for the synthesis of N-(diisopropyl phosphoryl)-trans-4-hydroxy-L-proline, substantially as hereinbefore described with reference to any one of the examples.

12. An N-(di-substituted phosphoryl)-trans-4-hydroxy-L-proline when produced by the process of any one of claims 1 to 7, 9 or 10.

13. N-(diisopropyl phosphoryl)-trans-4-hydroxy-L-proline when produced by the process of claim 8 or claim 11.

Dated 3 May, 1999
Merck & Co., Inc.

Patent Attorneys for the Applicant/Nominated Person
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