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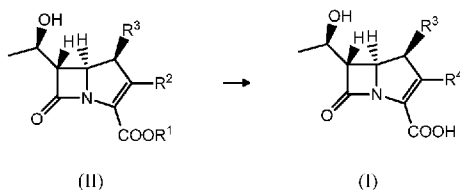
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MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,(54) Title: PROCESS FOR THE DEPROTECTION OF A CARBAPENEM BY HETEROGENEOUS CATALYTIC HYDRO-
GENATION WITH HYDROGEN IN THE PRESENCE OF AN ORGANIC AMINE(57) Abstract: 201600080 17 Process for preparing a carbapenem Abstract
Process for preparing a carbapenem or precursors thereof (I) by cleaving one
or more protecting groups of a substance (II) 5 comprising the steps of: a) hy-
drogenating with hydrogen a reaction mixture (1) comprising the substance (II),
at least 10 one organic solvent and at least one aromatic amine in the presence
of a heterogeneous hydrogenation catalyst to form a product mixture (1), b) re-
moving the heterogeneous catalyst from the product mixture (1) to form a prod-
uct mixture (2), c) adding water to the product mixture (2), wherein the ratio by
weight of water added to the 15 product mixture (2) is from 0.1 to 10, d) thermal
treatment of the product mixture (2) to form a product mixture (3) comprising
substance (I).

PROCESS FOR THE DEPROTECTION OF A CARBAPENEM BY HETEROGENEOUS CATALYTIC
HYDROGENATION WITH HYDROGEN IN THE PRESENCE OF AN ORGANIC AMINE

The present invention relates to a process for preparing a carbapenem.

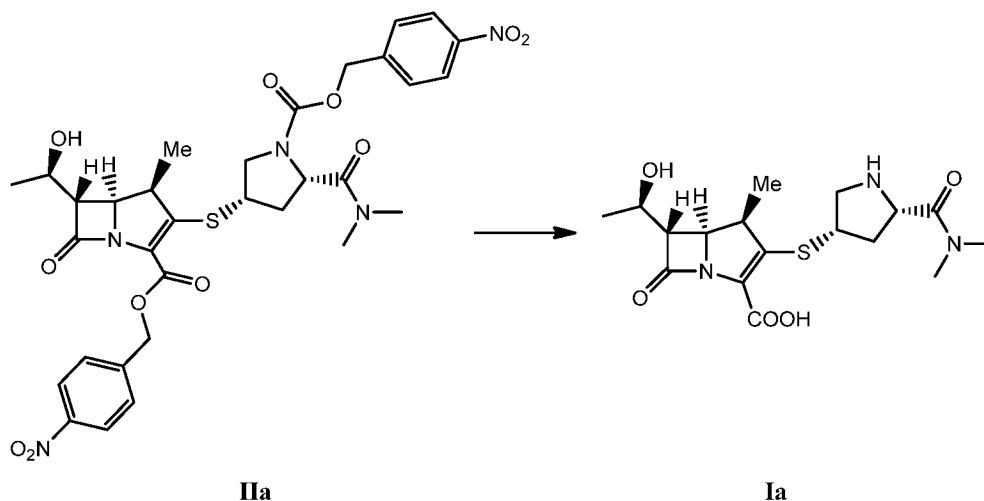
Carbapenems are β -lactam antibiotics which are used as medicaments due to their broad antimicrobial spectrum of activity. Representatives of this substance class are, for example,

5 meropenem, imipenem, ertapenem, doripenem, tebipenem, biapenem and panipenem.

Numerous preparation processes are known for these compounds, wherein these compounds are typically synthesized via multi-stage methods. An important step in many syntheses is the removal of protecting groups, also known as deprotection. Important representatives of protecting groups in this case are unsubstituted and substituted benzyl or benzyloxycarbonyl groups such as, for

10 example, p-nitrobenzyl (PNB) and p-nitrobenzyloxycarbonyl (PNZ = CO₂PNB). To prepare carbapenems, various methods for removing protecting groups are known from the prior art.

Shown below is a general reaction scheme for preparing meropenem (**Ia**) by removing PNZ and PNB protecting groups from the protected meropenem derivative (**IIa**):



15 US4933333 discloses a process for preparing β -lactam compounds. A method for the reductive removal of substituted benzyl and benzyloxycarbonyl protecting groups, p-nitrobenzyl and p-nitrobenzyloxycarbonyl respectively, is described inter alia. In example 2, a protected meropenem derivative is dissolved in a mixture of THF and ethanol and morpholinopropanesulphonic acid buffer and hydrogenation catalyst are added. The reaction mixture is hydrogenated, the catalyst is

20 filtered off and THF and ethanol are distilled off. The residue is washed with ethyl acetate and the solvent again distilled off. The aqueous solution is purified by polymer chromatography to obtain the deprotected product, meropenem. From the data, a very low concentration of the protected meropenem derivative can be calculated. It is less than 1% by weight in a mixture of THF/ethanol/buffer solution. In this reaction, therefore, a considerable amount of solvent is required

25 per mole of product; in example 2 > 60 mL of solvent/mmol of product. This has a direct influence on the production costs.

CN102336756 discloses a method for preparing meropenem by reductive deprotection in a one-stage reaction. The reaction is carried out in a refluxing organic solvent in the presence of a

hydrogenation catalyst at standard pressure, wherein additionally water may be added. It is possible to use Pd, Pd/C, palladium hydroxide or Raney nickel as catalysts. Formic acid or ammonium formate are used as reducing agent. Alcohols, ethers or esters are suitable as solvent. A yield of ca. 50% is obtained and the concentration of protected meropenem is 3.5% by weight in THF/water in example 1 and ca. 3.7% by weight in methanol/water in example 2. No hydrogen is used as reducing agent in the reaction. A considerable amount of solvent per mole of product is also required in this case.

CN103450203 discloses a method for preparing meropenem by one-pot synthesis of a protected meropenem derivative and subsequent removal of a PNB and a PNZ protecting group. Tetrahydrofuran and/or N,N-dimethylformamide is used as solvent. The reduction is effected with hydrogen and Pd/C as catalyst. After removal of the catalyst, meropenem is crystallized by adding acetone or tetrahydrofuran. In examples 1-5, a yield between 69% and 78 mol% is obtained.

WO2007/104221 discloses a method for preparing meropenem, in which the reductive removal of a PNB and a PNZ protecting group is carried out in a one-stage reaction in an organic-aqueous solvent in the presence of a base and a catalyst, Pd/C, at a temperature in the range of 0-100°C. A yield of 65% in example 2 and 71.8% in example 3 is achieved. The concentration of starting material can be calculated as ca. 3.0% by weight in example 2 and ca. 2.4% by weight in example 3. The molar amount of 2,6-dimethylpyridine used as base relative to the molar amount of product obtained can be calculated for example 2 and 3 as 4.4 mol/mol in example 2 and 5.0 mol/mol in example 3. By means of the reaction regime with a THF-water mixture, only a very low reactant concentration can be used. This results in a considerable requirement of organic solvents per gram of starting material (> 90 mL/mmol of meropenem in examples 2 and 3). This has a direct influence on the production costs.

The object of the present invention is therefore to provide an economical deprotection method that is simple to carry out for preparing a carbapenem, in which, inter alia, a minimal amount of starting materials would be used.

It has now been found that the preparation of carbapenems by a two-stage reaction regime for deprotection is significantly more economical than the methods described in the prior art.

From the prior art, all methods for preparing carbapenems by removal of protecting groups describe a one-stage hydrogenation/deprotection reaction, wherein a solution of protected carbapenem is hydrogenated and is then directly worked-up. This typical procedure has some disadvantages. Deprotection methods using solid heterogeneous hydrogenation catalysts, in which a relatively large amount of water is added to the reaction mixture before the reduction, is a common embodiment. Firstly, the solubility of the starting material in a water-solvent mixture is usually very limited such that only a low concentration of the starting material can be achieved and, as a consequence, a lot of solvent is required per unit weight of product. This can considerably increase the production costs of the product. Secondly, the different solubility of the starting materials, products and intermediates in a water-solvent mixture can mean that some of the

product or intermediate may already precipitate during the catalytic conversion. This makes the separation of the product from the solid hydrogenation catalyst more difficult and may lead to a yield loss of the carbapenem target product.

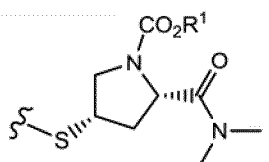
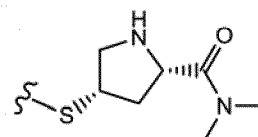
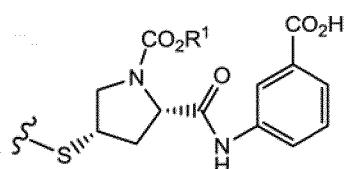
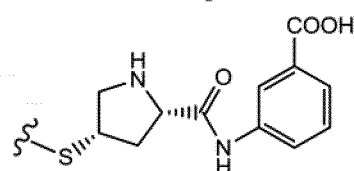
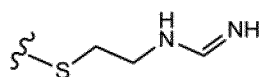
5 In the process according to the invention, lower amounts of organic solvent are required. In addition, the reaction can be carried out in this manner in a much broader concentration range. It is thus possible, for example, to increase considerably the concentration of the protected starting material and at the same time not to negatively influence conversion and yield.

The invention relates to a process for preparing a substance of the formula (I) from a substance of the formula (II):

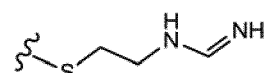
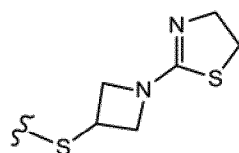
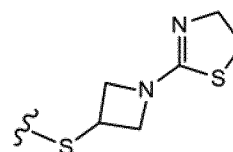
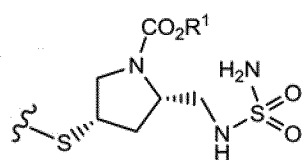
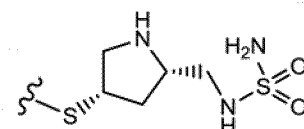
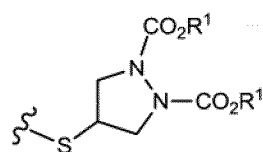
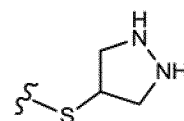
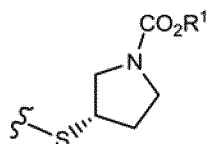


(II)

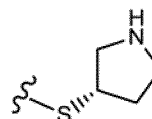
(I)

 $R^1 = \text{p-nitrobenzyl}$ $R^2 =$ $R^3 =$ $R^4 =$ CH₃**Ia: Meropenem**CH₃**Ib: Ertapenem**

H

**Ic: Imipenem**CH₃**Id: Tebipenem**CH₃**Ie: Doripenem**CH₃**If: Biapenem precursor**

H

**Ig: Panipenem precursor**

comprising the steps of:

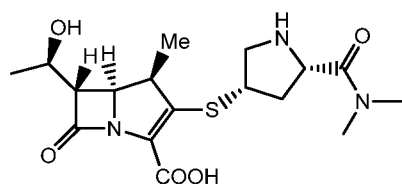
- a) hydrogenating with hydrogen a reaction mixture (1) comprising substance (II), at least one organic solvent and at least one aromatic amine in the presence of a heterogeneous hydrogenation catalyst to form a product mixture (1),
- 5 b) removing the heterogeneous catalyst from the product mixture (1) to form a product mixture (2),
- c) adding water to the product mixture (2), wherein the ratio by weight of water added to the product mixture (2) is from 0.1 to 10,
- 10 d) thermal treatment of the product mixture (2) to form a product mixture (3) comprising substance (I).

Substance (I) is a carbapenem (**Ia-Ie**) or synthetic precursor thereof (**If, Ig**) and substance (II) is a corresponding p-nitrobenzyl and/or p-nitrobenzyloxycarbonyl protected carbapenem precursor.

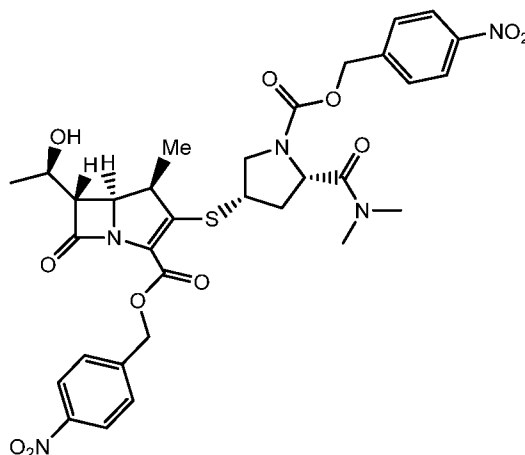
- 15 The deprotection of a protected carbapenem or precursor thereof, the substance (II), is a complex procedure in which, inter alia, the solubility of the reactant used and of the intermediates formed and also of the target product, substance (I), play an important role. The first phase of the process, the catalytic hydrogenation of a substance (II) dissolved in organic solvent to form the primary intermediates, proceeds optimally if no or as little water as possible is added to the reaction mixture
- 20 (1) and the constituents of the product mixture (1) remain dissolved except the heterogenous catalyst used. There were indications that water promotes the decomposition of the intermediates formed during the catalytic hydrogenation to the target product, substance (I). The solubility of the substance (I) in an organic-aqueous solvent mixture is very limited which may lead to yield losses, particularly at relatively high concentrations, by removal together with the the solid catalyst. For this
- 25 reason, water is added to the product mixture (1) only after removal of the catalyst. During the thermal treatment, the intermediates are specifically converted to the target product. A two-stage process procedure of this kind has great advantages compared to the methods known from the prior art.
- 30 By means of this two-stage reaction regime, a higher concentration of substance (II) in the reaction mixture can be achieved.

- The process is suitable for preparing the substances (I) such as, for example, meropenem (Ia), ertapenem (Ib), imipenem (Ic), tebipenem (Id), doripenem (Ie) and the synthetic precursors of
- 35 biapenem (If) and panipenem (Ig) from the corresponding p-nitrobenzyl (PNB) and/or p-nitrobenzyloxycarbonyl (PNZ) protected derivatives (II).

Preferably, meropenem (Ia) can be prepared in this way from the corresponding protected meropenem derivative (IIa):



Ia



IIa

The process according to the invention preferably comprises an additional step to be carried out after step d) in which a liquid precipitant is added to the product mixture (3) and the solid substance (I) is separated off.

- 5 To isolate the solid substance (I), other methods may also be used such as, for example, partial evaporation of the solvent in combination with precipitation.

The reaction mixture (1) comprises the substance (II), at least one organic solvent and at least one aromatic amine. The solvent for the solution comprising the substance (II) may be an organic solvent or a solvent mixture of this solvent with water or other organic solvents. The organic solvent is preferably selected from the group consisting of tetrahydrofuran (THF), dioxane, diethyl ether, N,N-dimethylformamide (DMF), alcohols, ethyl acetate and mixtures thereof. Particular preference is given to THF and mixtures thereof with ethanol or methanol. The reaction mixture (1) without substance (II) and amine preferably consists of more than 80% by weight, preferably at least 90% by weight, particularly preferably 95% by weight or more of an organic solvent and at most 20% by weight, preferably less than 10% by weight, particularly preferably 0 to 5% by weight of water.

The water content of the solution should be as low as possible in order to enable as high a concentration as possible of the substance (II) readily soluble in the organic solvent. Therefore, preferably no water is used if possible.

- 20 Due to the residual moisture content of the solid heterogeneous hydrogenation catalyst, low amounts of water may be present in the reaction mixture (1).

The reaction mixture (1) preferably comprises 1 to 50% by weight, preferably 3 to 40% by weight, particularly preferably 5 to 30% by weight of the substance (II).

- 25 All solid hydrogenation catalysts suitable for this purpose may be selected as solid heterogeneous hydrogenation catalyst. Preference is given to using those hydrogenation catalysts which contain at least one catalytically active metal. Preferably, the catalytically active metal is one of groups VII B and/or VIII B of the Periodic Table of the Elements, with precious metals and Ni being preferred, and Ru, Rh, Pd, Pt, Re and Ni being particularly preferred. The metals may be present in the hydrogenation catalyst as they are and/or in the form of oxides, hydroxides, salts or complexes.

The catalytically active metal may be used either applied to a support or alone, for example as particles. The support material is unrestricted; typically, supports such as aluminium oxide, silicon dioxide, iron oxide, magnesium oxide, zirconium dioxide, titanium dioxide, cerium oxide, activated carbon, graphite, carbon black or similar supports known to the person skilled in the art in the field of hydrogenation are used. The content of catalytically active metal on the support is selected typically within a range from 0.1% by weight to 30% by weight, based on the total weight of the catalyst. Preferably, a content of 1% by weight to 15% by weight of catalytically active metal on the support is selected.

Examples of such hydrogenation catalysts are Pt/C, Pd/C, Rh/C, Ru/C, Pd/CaCO₃, Pt/Al₂O₃, Pd/Al₂O₃, Ru/Al₂O₃, Rh/Al₂O₃, Pd/Re/C, Pt/Re/C, Pt/V/C, Pt/Fe/C, RuO₂, Raney nickel. Preferably, the hydrogenation catalyst is selected from the group consisting of Pd/C, Pt/C, Pd/Al₂O₃, Pt/Al₂O₃, Pd/CaCO₃, Ru/Al₂O₃, Pd/Re/C, Pt/Re/C, Pt/V/C, Pt/Fe/C and Raney nickel. Particular preference is given to Pd/C with 5-10% by weight Pd and Pt/C with 5-10% by weight Pt, with Pd/C with 5% by weight Pd (5% Pd/C) and Pt/C with 5% by weight Pt (5% Pt/C) being especially preferred.

The amount of solid heterogeneous hydrogenation catalyst can be freely selected by the person skilled in the art, where the molar ratio of catalytically active metal of the hydrogenation catalyst to substance (II) is typically in a range from 1:1 to 1:10 000. Further preference is given to a range from 1:10 to 1:1000, particular preference being given to a range from 1:20 to 1:300.

The solid heterogeneous hydrogenation catalyst may be used with a residual moisture content, wherein the residual moisture content is specified by the loss on drying. The loss on drying can be in the range of 0% by weight to 80% by weight, a loss on drying in the range of 0% by weight to 65% by weight being preferred.

The aromatic amine is preferably selected from the group consisting of aniline, substituted anilines (aminobenzene derivatives), polyaromatic amines, heteroaromatic amines (such as aminopyridines, aminothiophenes, aminofurans etc.), which may be further substituted. Particular preference is given to using anilines such as aniline, 4-ethylaniline, p-aminotoluene, m-aminotoluene, o-aminotoluene, particular preference being given to using p-aminotoluene.

The molar ratio [the aromatic amine added to the reaction mixture (1) / [substance (II)] is preferably from 0.1 to 20, preferably from 0.5 to 10, particularly preferably from 1 to 7.

Hydrogen pressure is not essential for the hydrogenation, although the reaction time can be shortened by means of an elevated pressure. The absolute reaction pressure is typically adjusted and maintained constant using a hydrogen source in a range of 1 to 200 bar, preferably 1.1 to 100 bar, and particularly preferably 2 to 20 bar. For the purpose of the conversion, hydrogen gas or a mixture of hydrogen gas with inert gas, e.g. commercially available forming gas of the composition 5% H₂/95% N₂, may be used. The preferred hydrogen source is hydrogen gas.

The temperature during the reaction with hydrogen can be freely selected by a person skilled in the art depending on the solvent and the thermal stability of the carbapenem derivative. A temperature

in the range of 0°C up to the boiling point of the selected solvent is typically set. The reaction with hydrogen is preferably carried out at a temperature in the range of 0 - 60°C, more preferable is a temperature in the range of 15 - 50°C, particularly preferable is a temperature in the range of 15 - 25°C. The reaction is typically terminated when no further H₂ uptake takes place. The H₂ uptake
5 can be monitored during the reaction using customary methods.

The solid heterogeneous hydrogenation catalyst can be removed from the product mixture (1) with the aid of any of the methods known to those skilled in the art for separating solids from liquids. Suitable methods are, e.g., filtration, centrifugation, sedimentation or ultrasound separation.

Water is added to the product mixture (2) after hydrogenation and removal of the catalyst in step c).
10 Here, the ratio by weight of water added to product mixture (2) is from 0.1 to 10, preferably from 0.3 to 7, particularly preferably from 0.5 to 5.

The temperature during the thermal treatment with water in step d) is preferably adjusted to values of 0 - 100°C, preferably 15 - 60°C, particularly preferably 25 - 50°C and particular preference is given to carrying out the reaction at 40°C. The mixture is optionally stirred during the reaction.
15 Thermal treatment in step d) is preferably carried out within a period of 0.1 to 10 hours, preferably 0.3 to 5 hours, particularly preferably within a period of 0.5 to 1.5 hours.

The precipitant serves the purpose of lowering the solubility of the substance (I) in the product mixture (3). Preference is given to using a solvent which is at least partially miscible with water. Particular preference is given to using an aprotic solvent as liquid precipitant. The precipitant is
20 particularly preferably selected from the group consisting of acetone and THF.

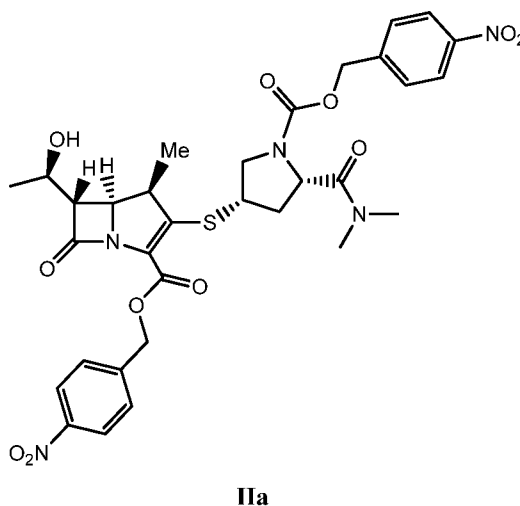
In order to achieve as complete a separation of the substance (I) from the product mixture (3) as possible, the product mixture (3) is preferably cooled after the thermal treatment in step d) and before addition of a precipitant. The temperature during the precipitation is preferably -30 to 30°C, particularly preferably -10 to +15°C. Methods for cooling are known to those skilled in the art.

25 The substance (I) can be separated from the product mixture with the aid of any of the methods known to those skilled in the art for separating solids from liquids. Suitable methods are filtration, centrifugation or sedimentation.

The isolated crude product comprising the substance (I) can be purified by customary methods and thus be obtained in the desired purity. The purification may comprise here at least one of the steps
30 commonly used by those skilled in the art, such as washing, extraction, recrystallization, filtration or drying.

EXAMPLES

Starting material



5 Analysis

To determine the loss on drying, the catalysts were dried to constant mass at 80°C in a vacuum drying cabinet (loss on drying (%) = (mass before drying – mass after drying)*100%/(mass before drying)).

The content of pure target product meropenem in the isolated and dried precipitate (crude product) was determined by HPLC (HPLC System 1100 Series with a DAD, Agilent, and a MultiPurpose Sampler 3, Gerstel) analogously to the procedure according to USP 38 (United States Pharmacopoeia) against meropenem trihydrate (USP Reference Standard) as external standard. All specified yields refer therefore to the isolated yields of target product meropenem determined by the purity of the isolated crude product.

15 1. Inventive examples

General experimental procedure (examples 1-14)

The solution, the catalyst and the auxiliary are weighed into a pressure reactor. The reactor is sealed, inertized with nitrogen and brought to the reaction temperature. The reactor is filled with hydrogen, the pressure in the reactor is adjusted to the reaction pressure with hydrogen and the stirrer is started. The reaction is terminated when no further H₂ uptake is observed. After inertization with nitrogen, the reactor is opened. The catalyst is removed from the reaction mixture using a filter.

For the workup and yield determination, a portion of the filtrate obtained is used. Deionized water is added with stirring to the filtered reaction mixture, this mixture being stirred for 1 h at 40°C.

25 Subsequently, the mixture is cooled in the ice bath to 0-5°C, and the mixture is stirred for one hour in the ice bath after addition of acetone in order to precipitate the reaction product. The precipitate thus precipitated is filtered off and dried at 35°C in the vacuum drying cabinet. The yield is

determined by determining the content of the isolated and dried precipitate by HPLC analogously to the procedure according to USP 38 against meropenem trihydrate (USP Reference Standard) as external standard.

5 2. Comparative examples

CE 1 - analogous to WO2007/104221 (one-stage reaction)

1.4 g of compound (IIa) are dissolved in 35 ml of THF and 28 ml of water are added with stirring. 6.0 g of this solution, 2,6-lutidine and catalyst (10% Pd/C from Evonik Industries) are weighed into a pressure reactor. The reactor is sealed, inertized with nitrogen and brought to the reaction
10 temperature. The reactor is filled with hydrogen, the pressure in the reactor is adjusted with hydrogen to 18 bar and the stirrer is started. The reaction is terminated after one hour. After inertization with nitrogen, the reactor is opened. The catalyst is removed from the reaction mixture using a filter.

For the product precipitation and yield determination, a portion (3.0 g) of the filtrate obtained is
15 used. 5.5 ml of acetone are added to the filtered reaction mixture. Product precipitation is effected by cooling in the ice bath at ca. 5°C. After 30 min, a further 2.7 ml of acetone are added dropwise at the same temperature. After 30 min, the precipitate is filtered off and dried at 40°C in the vacuum drying cabinet. The yield is determined by determining the concentration of the aqueous solution of the dried precipitate by HPLC analogously to the procedure according to USP 38 against
20 meropenem trihydrate (USP Reference Standard) as external standard.

CE 2: The experiment is carried out analogously to *CE 1* but using Pd/C with 5% by weight Pd as catalyst.

CE 3: The experiment is carried out according to the general experimental description for the inventive examples but using 2,6-lutidine instead of p-aminotoluene.

25 *CE 4*: The experiment is carried out according to the general experimental description for the inventive examples but using n-butylamine.

CE 5: The experiment is carried out according to the general experimental description for the inventive examples but using ethylenediamine.

30 *CE 6*: The experiment is carried out according to the general experimental description for the inventive examples but no amine is used.

CE 7: The experiment is carried out according to the general experimental description for the inventive examples but no amine is used.

The starting materials and reaction conditions can be found in Table 2.

Table 1: Starting materials and reaction conditions - inventive examples

Exempl e	Solution IIa in THF		Aromatic amine	Hydrog enation time ^[f]	Amine / IIa ^[k]	Catalyst	Product mixture (2)	Water ^[d]	Water/ product mixture (2) ^[j]	Aceton e	Yield	SolMi/la ^[l]
	g	% by weight IIa										
1	5.38	7.25	p-aminotoluene 0.8	36	1.4	31 ^[a]	2.74	3.0	1.1	8.0 ^[e]	79	40
2	5.56	11.3	p-aminotoluene 1.0	30	1.1	51 ^[a]	2.76	5.0	1.8	13.5 ^[e]	79	38
3	5.67	17.0	p-aminotoluene 1.6	22	0.7	50.3 ^[a]	2.71	8.0	3.0	21.5 ^[e]	70	43
4	5.61	18.4	p-aminotoluene 1.6	41	1.1	80.6 ^[a]	2.91	8.0	2.7	21.5 ^[e]	80	32
5	5.61	18.4	p-aminotoluene 3.2	41	2.2	82 ^[a]	2.85	8.0	2.8	21.5 ^[e]	77	35
6	5.62	18.4	p-aminotoluene 4.0	41	2.7	82 ^[a]	2.84	8.0	2.8	21.5 ^[e]	84	33
7	5.85	18.4	o-aminotoluene 1.6	35	1.0	81 ^[a]	2.79	8.0	2.9	21.5 ^[e]	80	34
8	5.70	18.4	m-aminotoluene 1.6	35	1.1	80 ^[a]	2.80	8.0	2.9	21.5 ^[e]	77	35
9	5.65	18.4	4-ethylaniline 1.6	40	1.1	80 ^[a]	2.70	8.0	3.0	21.5 ^[e]	75	37
10	5.58	18.4	aniline 1.6	40	1.1	81 ^[a]	2.74	8.0	2.9	21.5 ^[e]	73	37
11	5.43	16.2 ^[g]	p-aminotoluene	27	1.3	86 ^[a]	2.73	8.0	2.9	21.5 ^[e]	82	38

[illegible]

[a] Pt/C with 5% by weight Pt, loss on drying = 66.0%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[b] Pd/C with 5% by weight Pd, loss on drying = 56.0%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[c] Pd/C with 10% by weight Pd, loss on drying = 56.5%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[d] stirring for 1 h at 40°C;

[e] stirring for 1 h in the ice bath;

[η] 25°C, 18 bar H₂

[g] in THF/EtOH (ratio by volume THF : EtOH = 2:1

[h] in THF/H₂O (ratio by volume THF : water = 1.25:1) corresponds to 4.50% based only on THF)

[i] in THF/EtOH (ratio by volume THF: EtOH = 2:1)

ratio by weight

[k] molar ratio

[I] total mass of all organic solvents in g (solvent in reaction mixture (1) + precipitant) with respect to the mole amount (mmol) of product formed

Table 2: Starting materials and reaction conditions - comparative examples

Exempl e	Solution IIa in THF		Base or Amine	Hydrog enation time ^[f]	Base or amine / IIa ^[k]	Catalyst	Product mixture (2)	Water ^[d]	Water/ product mixture (2) ^[j]	Acetone	Yield	SoIMI/IIa ^[i]
	g	% by weight IIa										
CE 1	6.00	2.37 ^[h]	2,6-lutidine 0.70	60	7.9	12 ^[c]	3.00	-	0.0	8.2	52	179
CE 2	6.00	2.37 ^[h]	2,6-lutidine 0.70	60	7.9	24 ^[b]	3.00	-	0.0	8.2	49	190
CE 3	5.58	18.2	2,6-lutidine 1.6	35	1.1	81 ^[a]	2.77	8.0	2.9	21.5 ^[e]	37	74
CE 4	5.61	18.2	n-butylamine 1.6	40	1.1	80 ^[a]	2.80	8.0	2.9	21.5 ^[e]	0.59	4600
CE 5	5.58	18.2	ethylenediamine 1.6	35	1.1	80 ^[a]	2.79	8.0	2.9	21.5 ^[e]	0	-
CE 6	5.45	7.12	-	90	2.9	30 ^[a]	2.76	2.0	0.7	21.5 ^[e]	60	116
CE 7	5.47	16.3 ^[i]	-	27	1.3	81 ^[a]	2.80	8.0	2.9	21.5 ^[e]	22	135

[a] Pt/C with 5% by weight Pt, loss on drying = 66.0%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[b] Pd/C with 5% by weight Pd, loss on drying = 56.0%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[c] Pd/C with 10% by weight Pd, loss on drying = 56.5%, the catalyst weight refers in each case to the catalyst dry substance, the catalyst is not dried before use;

[d] stirring for 1 h at 40°C;

[e] stirring for 1 h in the ice bath;

[f] 25°C, 18 bar H₂

[g] in THF/EtOH (ratio by volume THF : EtOH = 2:1

[h] in THF/H₂O (ratio by volume THF : water = 1.25:1) corresponds to 4.50% based only on THF)

[i] in THF/EtOH (ratio by volume THF: EtOH = 2:1)

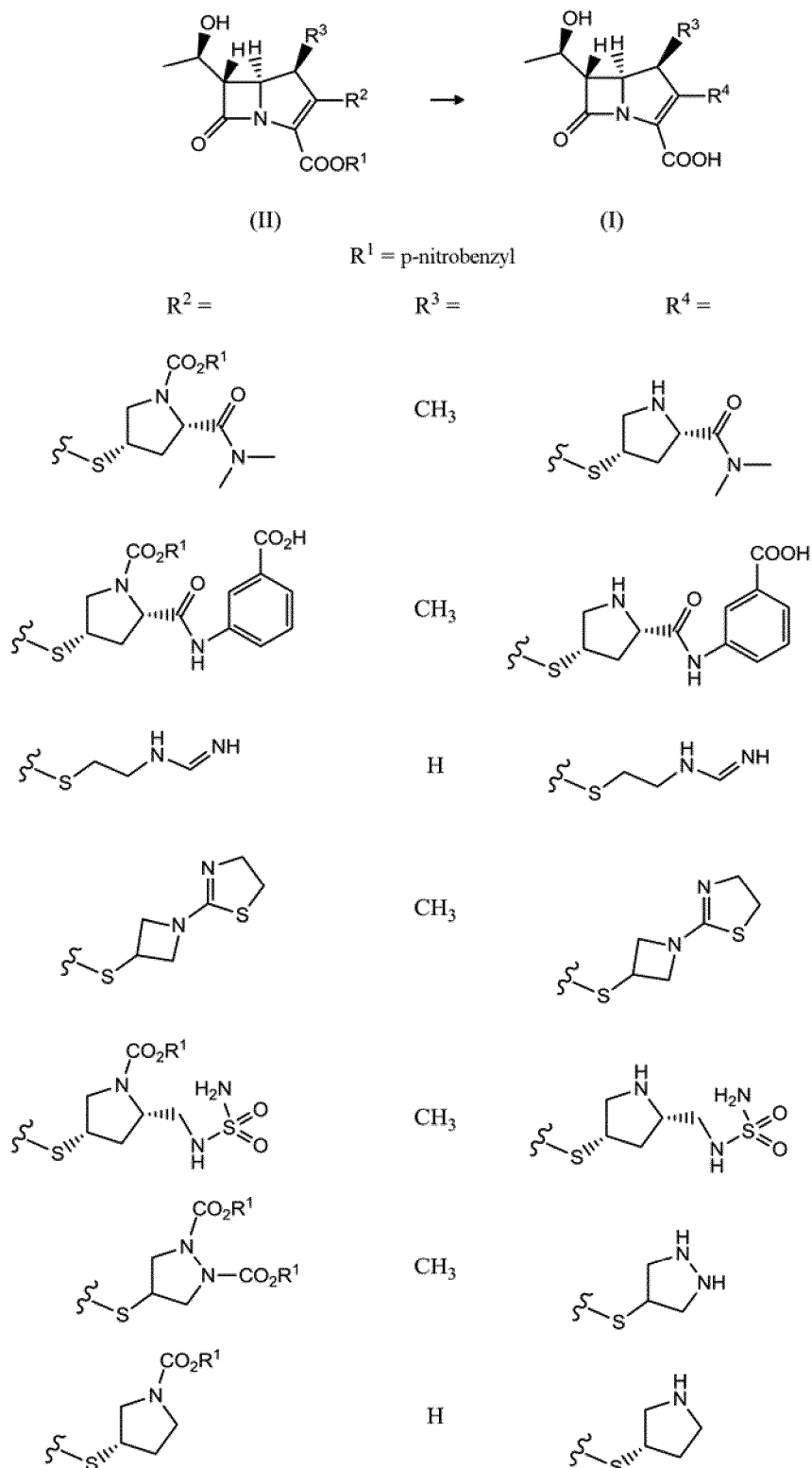
[j] ratio by weight

[k] molar ratio

[l] total mass of all organic solvents in g (solvent in reaction mixture (1) + precipitant) with respect to the mole amount (mmol) of product formed

Claims

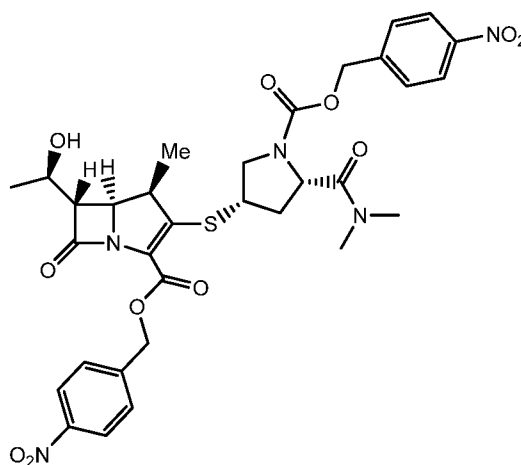
1. Process for preparing a substance of the formula (I) from a substance of the formula (II):



comprising the steps of:

- a) hydrogenating with hydrogen a reaction mixture (1) comprising substance (II), at least one organic solvent and at least one aromatic amine in the presence of a heterogeneous hydrogenation catalyst to form a product mixture (1),
- b) removing the heterogeneous catalyst from the product mixture (1) to form a product mixture (2),
- c) adding water to the product mixture (2), wherein the ratio by weight of water added to the product mixture (2) is from 0.1 to 10,
- d) thermal treatment of the product mixture (2) to form a product mixture (3) comprising substance (I).

2. Process according to Claim 1, characterized in that substance (II) is



and substance (I) is meropenem.

3. Process according to Claims 1 or 2, characterized in that after step d) a liquid precipitant is added to the product mixture (3) and the solid substance (I) is separated off.
4. Process according to Claims 1 to 3, characterized in that the organic solvent is selected from the group consisting of tetrahydrofuran, dioxane, diethyl ether, N,N-dimethylformamide, ethyl acetate, methanol, ethanol, propanol and mixtures thereof.
5. Process according to Claims 1 to 4, characterized in that the hydrogenation is carried out at a reaction pressure of 1 bar to 200 bar.
6. Process according to Claims 1 to 5, characterized in that the heterogeneous hydrogenation catalyst is a Pd/C catalyst with 1-15% by weight Pd or a Pt/C catalyst with 1-15% by weight Pt.

7. Process according to Claims 1 to 6, characterized in that the heterogeneous hydrogenation catalyst is used in a molar ratio of catalytically active metal of the catalyst to substance (II) of from 1:1 to 1:10 000.
8. Process according to any of Claims 1 to 7, characterized in that the aromatic amine is selected from the group consisting of anilines, polyaromatic amines and heteroaromatic amines.
9. Process according to Claims 1 to 8, characterized in that the molar ratio of the aromatic amine added to the substance (II) is from 0.1 to 20.
10. Process according to Claims 3 to 9, characterized in that the precipitant is an aprotic solvent which is at least partially miscible with water.
11. Process according to Claims 1 to 10, characterized in that the reaction mixture (1) without substance (II) and amine consists of 0 to 20% by weight water.
12. Process according to Claims 1 to 11, characterized in that the product mixture (2) is treated thermally at temperatures of 0 to 100°C.
13. Process according to Claims 1 to 12, characterized in that the thermal treatment of product mixture (2) takes place within a period of 0.1-10 hours.
14. Process according to Claims 1 to 13, characterized in that the product mixture (3) after step d) is cooled to -10 to +15°C.
15. Process according to Claims 1 to 14, characterized in that the reaction mixture (1) comprises 5 to 50% by weight of the substance (II).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/066235

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D477/08 C07D477/20 A61K31/407 A61K31/04
ADD.

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/038700 A1 (LONG LISONG [CN] ET AL) 5 February 2015 (2015-02-05) examples 6-12	1-15
A	----- WO 2007/104221 A1 (SHENZHEN HAIBIN PHARMACEUTICAL [CN]) 20 September 2007 (2007-09-20) cited in the application examples 2,3 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

9 August 2017

Date of mailing of the international search report

23/08/2017

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/066235

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2015038700 A1	05-02-2015
		WO 2013143266 A1	03-10-2013

WO 2007104221 A1	20-09-2007	NONE	
