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(54) Benævnelse: **Fremgangsmåde til syntetisering af sapropterindihydrochlorid**

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DESCRIPTION

Technical field of the invention

[0001] The present invention relates to a method for synthesizing a medicine for treating Phenylketonuria (PKU), and particularly to a method for synthesizing sapropterin dihydrochloride.

Backpround of the invention

[0002] Sapropterin dihydrochloride, chemical name (6R)-2-amino-6-[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1H)-pteridinone dihydrochloride, molecular formula $C_9H_{15}N_5O_3 \cdot 2HCl$, and CAS registry number 69056-38-28, is a synthetic product of tetrahydrobiopterin (BH_4) dihydrochloride. BH4 is a cofactor of Phenylalanine Hydroxylase (PAH). Tyrosine is acquired from Phenylalanine (Phe) through hydroxylation under the action of PAH which is low in activity or even inactive in PKU patients, while BH_4 is able to activate PAH, promote normal oxidative metabolism of Phe in the bodies of the patients, and reduce the Phe levels in the bodies of some patients. On December 16th, 2007, the sapropterin dihydrochloride tablets produced by BioMarin Pharmaceutical Inc. in USA were approved by the Food and Drug Administration (FDA) for marketing for treatment of PKU. Because of the effective activity of sapropterin dihydrochloride, it is extremely necessary to select a route applicable to industrial production with high product purity.

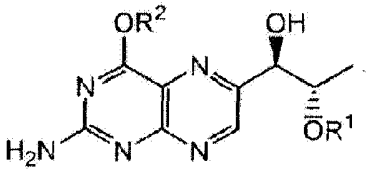
[0003] At present, BH_4 is mainly synthesized by the following methods reported in literatures:

1. 1. Preparation using 4-hydroxy-2,5,6-triaminopyrimidine (ATP) and 5-deoxy-L-arabinose as raw materials, please see literature E.L.Patterson et al., J.Am.Chem.Soc.78, 5868 (1956).
2. 2. Preparation using TAP and 5-deoxy-L-arabinose phenylhydrazone as raw materials, please see literature Matsuura et al., Bull.Chem.Soc.Jpn., 48,3767 (1975);
3. 3. Preparation by reaction of raw materials hydroxyl-protected TAP and 4-acetyl-2,3-epoxypentanal through oxidation of iodine and a dehydroxylation protecting group, please see literature Matsuura et al., Chemistry of Organic Synthesis,Ml/g.46.No.6,P570 (1988).

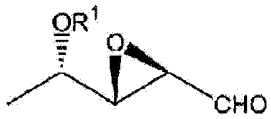
[0004] These traditional methods for preparing BH4 have the following major disadvantages: raw materials are expensive, arabinose which can be hardly acquired is used as a carbon atom radical for asymmetric synthesis; there are multiple steps in reactions with low yield, and low product purity, 5-deoxy-L-arabinose is easily degraded in a reaction solution, and products

of the synthesis routes above have low stereoselectivity. To sum up, the traditional synthesis methods are not applicable to mass industrial production. Therefore, a synthesis route, which is applicable to industrial production with high product purity, high yield and high stereoselectivity, needs to be searched urgently.

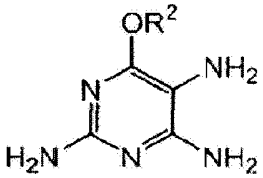
WO 2009/047902 A1 discloses a method which enables to commercially produce a pteridine compound with high yield. Specifically, it discloses a method for producing a pteridine compound represented by the general formula (3)



which is characterized in that an optically active epoxy aldehyde compound represented by the general formula (1)



and a pyrimidine compound represented by the general formula (2)



are condensed in a polar solvent in the presence of an acid having a pKa of not more than 4.5, and then the resulting compound is subjected to oxidation.

WO 2005/049614 A2 discloses a process for the preparation of tetrahydrobiopterin from neoprerin and/or 6-substituted pterins with an improved yield and a high stereoselectivity. Also disclosed are novel individual intermediates useful for the preparation of tetrahydrobiopterin, such as selectively protected neopterin.

JP 2575781 B discloses production of L-bioprerin. To obtain the title compound, useful as a precursor of (6R)-tetrahydrobiopterin (remedy for Parkinson's disease), from an inexpensive raw material in good yield, an alkyl (S)-lactate is used as a starting raw material, passing through several novel intermediates.

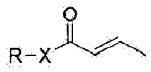
Summary of the invention

[0005] The present invention provides a method for synthesizing a sapropterin dihydrochloride compound. The present invention reduces a synthesis route of sapropterin dihydrochloride, and resolves a racemate intermediate or an intermediate having a low antimer isomerism value by using a chiral resolving reagent, thereby obtaining an intermediate having

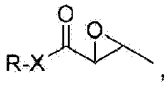
a high antimer isomerism value. Raw materials are cheap and readily available, and the cost is significantly reduced, hence providing an effective scheme for mass industrial production of sapropterin dihydrochloride.

[0006] The present invention provides a method for synthesizing sapropterin dihydrochloride, characterized in that it comprises the following steps:

Step 1: a compound 1 of the formula

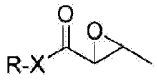


is subjected to epoxidation to generate a compound 2 of the formula

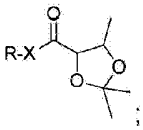


wherein X=NH or O, R=C1-C6 alkane or benzyl;

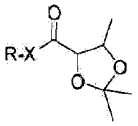
Step 2: in the presence of acetone, a Lewis acid, an inorganic base liquid, the compound 2 of the formula



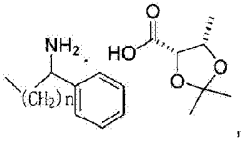
reacts to generate a compound 3 of the formula



Step 3: the compound 3 of the formula

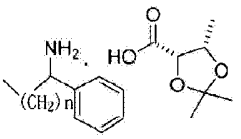


reacts in an alkaline solution, a polar solvent is used to dissolve a filter cake obtained through centrifugation, then a resolving reagent is added to perform resolution to obtain a compound 4 of the formula

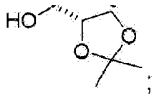


wherein n=0,1;

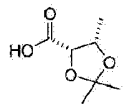
Step 4: dissolving the compound 4 of the formula



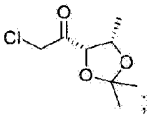
in an ether solvent, and performing separation in acidic conditions to obtain an organic phase, and adding N,N-diisopropylethylamine to the organic phase to obtain a compound 5 of the formula



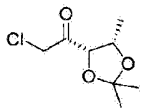
Step 5: using the compound 5 of the formula



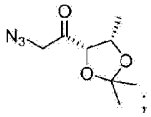
as a raw material to synthesize a compound 6 of the formula



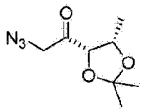
Step 6: reacting the compound 6 of the formula



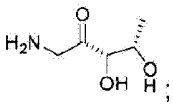
with a trinitride to generate a compound 7 of the formula



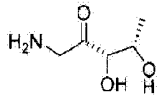
Step 7: subjecting the compound 7 of the formula



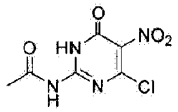
to hydrogenation to obtain a compound 8 of the formula



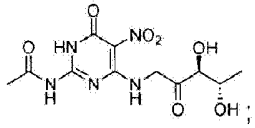
Step 8: reacting the compound 8 of the formula



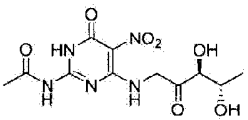
and a compound A of the formula



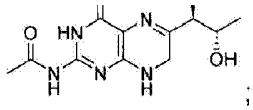
to generate a compound 9 of the formula



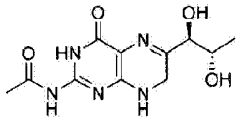
Step 9: subjecting the compound 9 of the formula



to cyclization to obtain a compound 10 of the formula



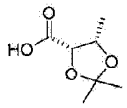
Step 10: adding a catalyst to the compound 10 of the formula



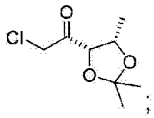
introducing hydrogen to perform a reaction, and then perform quenching in hydrochloric acid having a concentration of 10% to 20% to obtain sapropterin dihydrochloride.

[0007] Also provided is a method for preparing (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone, characterized in that it comprises the following steps:

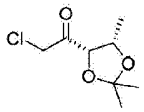
Step 1: using a compound 5 of the formula



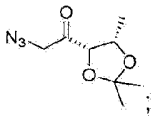
as a raw material to synthesize a compound 6 of the formula



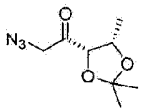
Step 2: reacting the compound 6 of the formula



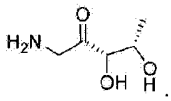
with a trinitride to generate a compound 7 of the formula



Step 3: subjecting the compound 7 of the formula



to hydrogenation to obtain a compound 8 of the formula



[0008] Preferred embodiments of the present invention are set forth in the dependent claims.

[0009] The present invention has the following advantages: 1. raw materials applied by the

synthesis method are readily available, and the cost is significantly reduced compared with the prior art; 2. the route of the present invention is simple, thus greatly reducing a synthesis route of sapropterin dihydrochloride; 3. technological conditions are stable, the whole operation process is simple with less discharge of waste water, waste gas, and waste residues, and less pollution, hence providing an effective scheme for mass industrial production of sapropterin dihydrochloride; 4. the present invention, which resolves a racemate intermediate or an intermediate having a low antimer isomerism value by using a chiral resolving reagent to obtain an intermediate having a high antimer isomerism value, is a supplement to a chiral route; 5. the present invention can obtain a target product with a purity higher than 98% and an enantiomeric excess as high as more than 98%.

Brief description of the drawings

[0010] The accompanying drawings of the specification are used for providing further understanding to the present invention and constitute a part of the present invention. The exemplary embodiments of the present invention and the illustrations thereof are used for explaining the present invention, instead of constituting an improper limitation to the present invention. In the accompanying drawings:

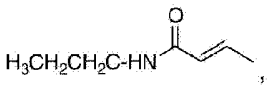
Fig. 1 is a flowchart of a chiral preparation process of a sapropterin dihydrochloride compound involved in the present invention.

Detailed description of the invention

[0011] It should be noted that, if there is no conflict, the embodiments in the present invention and the characteristics in the embodiments can be combined with one another. The present invention will be described in details below with reference to the accompanying drawings and in combination with the embodiments.

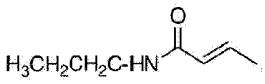
[0012] The ranges in the embodiments are caused by certain fluctuation of the temperatures and pH values as reactions progress in an experiment.

[0013] Embodiment 1: main raw material:



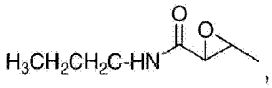
R=-$CH_2CH_2CH_3$ and X=NH

Step 1: add 950L(10g/ml) of pure water, and 95kg(1 eq) of crotonyl propylamine

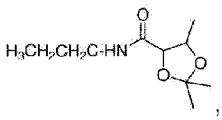


to a 2000L reaction kettle, increase the system temperature to 40±5°C, add 208kg(1.5eq) of N-bromobutanimide, react for 3 hours while preserving the temperature, add 300kg(1.5eq) of a sodium hydroxide solution having a concentration of 15% to the system, react for 3.5 hours while preserving the temperature, perform extraction and concentration to obtain 67.6kg of a compound 2,3 epoxy-butyryl propylamine, with a yield of 63%;

Step 2: in the presence of 219 kg of (8eq) acetone, add 25kg(0.4eq) of aluminium chloride to a 2000L reaction kettle, control the temperature at 20±5°C, add 67.6kg(1.0eq) of 2,3 epoxy-butyryl propylamine

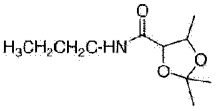


react for 8 hours while preserving the temperature, add 939kg of a sodium carbonate (1.5eq) solution having a concentration of 8% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 75.1 kg of 2,3-acetonide-propylbutyramide

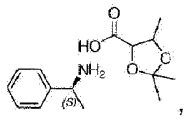


with a yield of 79%;

Step 3: add 450.6(6ml/g) of tetrahydrofuran, and 75.1 kg(1 eq) of 2,3-acetonide-propylbutyramide

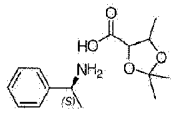


to a 1000L reaction kettle, increase the temperature to 30±5°C, add 11.3kg(1.2eq) of pure water and 117.2kg(1.2eq) of a methanol solution of sodium methoxide having a concentration of 29%, react for 6 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 525.7L (7 ml/g) of tetrahydrofuran, add 127.1 kg(2eq) of L-α-phenylethylamine, preserve the temperature at 22±5°C for 4 hours, and perform centrifugation and drying to obtain 27.3kg of 1-phenylethanamine 2,2,5-trimethyl-1,3-dioxolane-4-carboxylate

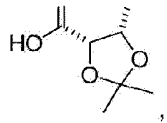


with a yield of 26%;

Step 4: add 28L(5ml/g) of 2-methyltetrahydrofuran, and 5.6kg (1eq) of 1-phenylethanamine 2,2,5-trimethyl-1,3-dioxolane-4-carboxylate

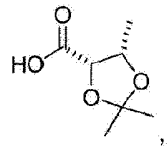


to a 72 L reaction bottle, then add a dilute hydrochloric acid aqueous solution having a concentration of 8% to the system to regulate the pH at 2±0.5, control the temperature at 0±5°C, react for 1 hour while preserving the temperature, perform liquid separation to obtain an organic phase, add 4.5kg of (1 eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 3.0kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid

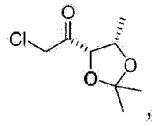


with a yield of 95%;

Step 5: add 30 L (10 ml/g) of 2-methyltetrahydrofuran, 3.0 kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid

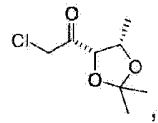


and 4.3kg(2eq) of N,N-diisopropylethylamine to a 72L reaction bottle, reduce the temperature to -20±5°C, add 2.7kg(1.3eq) of ethyl chloroformate, react for 1.5 hours while preserving the temperature, introduce a diazomethane gas for 1.5 hours, add 10.3kg (3eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 1.5 hours, add triethylamine to regulate the pH value to 8±0.5, and perform extraction, liquid separation and concentration to obtain 3.1 kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

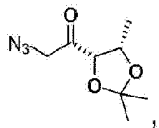


with a yield of 85%;

Step 6: add 31L(10ml/g) of acetone, 3.1 kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

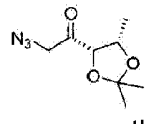


1.9kg(1.8eq) of sodium azide, and 0.5kg (0.2eq) of sodium iodide to a 72L bottle, react the system for 25 hours while preserving the temperature at 30±5°C, perform filtering and concentration to obtain an acetone solution containing 3.05kg of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

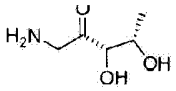


with a yield of 95%;

Step 7: add 30.5L (10ml/g) of tetrahydrofuran, 4.4kg(1.1eq) of triphenylphosphine, and 0.3kg (1.1 eq) of water to a 100L reaction kettle, regulate the pH of the system to 3±0.5 with citric acid, add the acetone solution containing 3.05kg (1 eq) of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

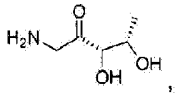


preserve the temperature at 20±5°C, react for 8 hours, perform suction filtration and concentration to obtain a filtrate containing 1.8kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

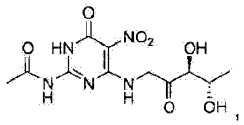


which is directly used in the next step, with a yield of 90%;

Step 8: add 18.9 L(9 ml/g) of isopropanol, 2.3 L (1.1ml/g) of pure water, 0.1 kg of (0.1 eq) of sodium iodide, 1.76kg(1.1 eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 0.92kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

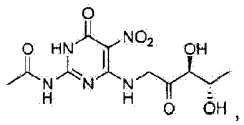


and 3.5kg(5eq) of triethylamine to a 50L reaction bottle, react the system for 6 hours while preserving the temperature at 50±5°C, then add a potassium dihydrogen phosphate-dipotassium hydrogen phosphate aqueous solution to regulate the pH of the system to 7±0.5; and filter the system to obtain 1.02kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

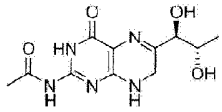


with a yield of 45%;

Step 9: add 2.0kg(1eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

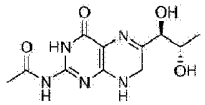


70L(35ml/g) of pure water and 0.6kg(0.3g/g) of Raney nickel to a 100L autoclave, introduce hydrogen until the pressure of the reaction system is 0.6±0.05MPa, control the temperature of the system at 20±5°C and the pressure at 0.6±0.05MPa, react for 20 hours, filter the system, and regulate the pH to 11.5±0.5 to obtain of an aqueous solution containing 1.7kg of acetylamino-7,8-dihydropteridine

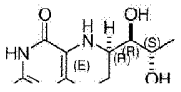


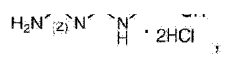
which is used directly in the next step;

Step 10: add 0.255kg(0.15g/g) of 20% palladium on carbon to the aqueous solution containing 1.7kg of acetylamino-7,8-dihydropteridine



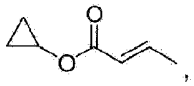
obtained in Step 9, introduce hydrogen until the pressure of the reaction kettle is 0.6±0.05MPa, control the temperature of the system at 20±5°C and the pressure at 0.6±0.05MPa, react for 80 hours, after reacting thoroughly, perform quenching in 10.29kg(7eq) of dilute hydrochloric acid having a concentration of 15%, and perform suction filtration and drying to the system to obtain a target product, i.e. a sapropterin dihydrochloride crude product of





recrystallize and purify the crude product by 25L (14.7ml/g) of methanol at 20±5°C to obtain 0.95kg of a pure product, with a yield of 50%, a purity of 98.5% and an enantiomeric excess of 99.2%.

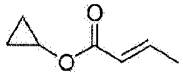
[0014] Embodiment 2: main raw material



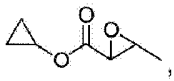
R=

and X=O

Step 1: add 2016L(20g/ml) of methanol, and 100.8kg(1eq) of crotonate cyclopropylalkyl ester

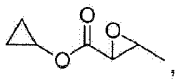


to a 3000 L reaction kettle, increase the system temperature to 50±5°C, add 414kg(3eq) of meta-chloroperoxybenzoic acid, react for 5 hours while preserving the temperature, add 673kg(3eq) of a potassium hydroxide solution having a concentration of 20% to the system, react for 4 hours while preserving the temperature, perform extraction and concentration to obtain 69.4kg of a compound 2,3 epoxy-cyclopropylalkyl butyrater

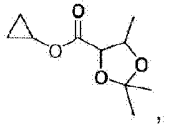


with a yield of 61%;

Step 2: in the presence of 425kg of (15eq) acetone, add 79.2kg(1 eq) of ferric chloride to a 2000L reaction kettle, control the temperature at 30±5°C, add 69.4kg(1.0eq) of 2,3 epoxy-cyclopropylalkyl butyrate

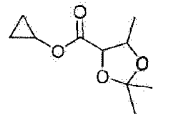


react for 10 hours while preserving the temperature, add 1552kg of a sodium carbonate (3eq) solution having a concentration of 10% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 75.3kg of 2,3-acetonide-cyclopropylalkyl butyrate

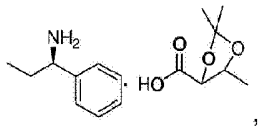


with a yield of 77%;

Step 3: add 753(10ml/g) of methanol, and 75.3kg(1 eq) of 2,3-acetonide-cyclopropylalkyl butyrate



to a 1000L reaction kettle, increase the temperature to 40±5°C, add 20.2kg(3eq) of pure water and 210kg(2eq) of a potassium hydroxide solution having a concentration of 20%, react for 8 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 753L (10ml/g) of methanol, add 322kg(5eq) of L-α-amphetamine, preserve the temperature at 30±5°C for 5 hours, and perform centrifugation and drying to obtain 27.2kg of



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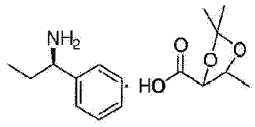
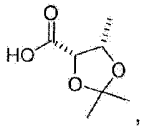
with a yield of 24.5%;

Step 4: add 27 L (10 ml/g) of tetrahydrofuran, 2.7 kg (1eq) of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-phenylpropylamino carboxylate



to a 72L reaction bottle, then add a dilute hydrochloric acid aqueous solution having a concentration of 10% to the system to regulate the pH at 3±0.5, control the temperature at 10±5°C, react for 1 hour, perform liquid separation to obtain an organic phase, add 6.1 kg of (3eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 1.3kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid



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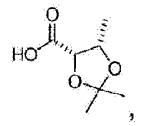
with a yield of 90%;

Step 5: add 20L(15 ml/g) of tetrahydrofuran, 1.3kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid



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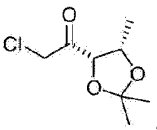
and 8kg(5eq) of N,N-diisopropylethylamine to a 72L reaction bottle, reduce the temperature to 0±5°C, add 2.9kg(3eq) of propyl chloroformate, react for 1 to 2 hours while preserving the temperature, introduce a diazomethane gas for 2 hours, add 12.7kg (5eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 2 hours, add sodium carbonate to regulate the pH value to 9±0.5, and perform extraction, liquid separation and concentration to obtain 1.3kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane



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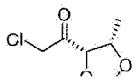
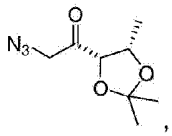
with a yield of 82%;

Step 6: add 19.5L(15ml/g) of acetonitrile, 1.3kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

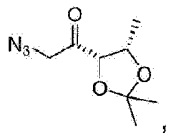


3.1 kg(4eq) of azidotrimethylsilane, and 0.8kg (0.8eq) of sodium iodide to a 72L bottle, react the system for 30 hours while preserving the temperature at 40±5°C, perform filtering and concentration to obtain an acetonitrile solution containing 1.21 kg of

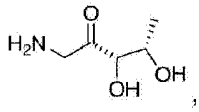


with a yield of 90%;

Step 7: add 18.2 L (15 ml/g) of 1,4-dioxane and 0.73 kg (0.6 g/g) of Raney nickel to a 50 L reaction kettle, introduce hydrogen until the system pressure is 0.9±0.1MPa, regulate the pH of the system to 1±0.5 with concentrated hydrochloric acid, add the acetonitrile solution containing 1.21 kg(1 eq) of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

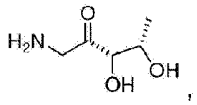


react at 30±5°C for 8 hours, perform suction filtration and concentration to obtain 0.71kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

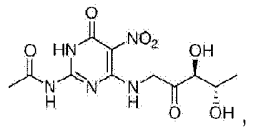


with a yield of 87.5%;

Step 8: add 47.5 L (15 ml/g) of methanol, 15.8L(5ml/g) of pure water, 1.28kg of (0.5eq) of potassium iodide, 3.6kg(1.5eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 1.4kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

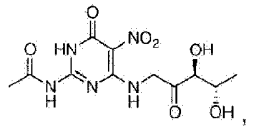


and 6.4 kg (8eq) of pyridine to a 100 L reaction bottle, react the system for 8 hours while preserving the temperature at 80±5°C, then add an ammonium formate-ammonia aqueous solution to regulate the pH of the system to 8±0.5; and filter the system to obtain 1.47kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one



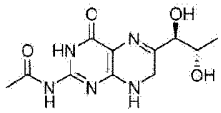
with a yield of 43.2%;

Step 9: add 2.94kg(1 eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one



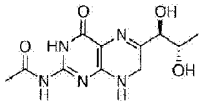
147L(50ml/g) of methanol and 1.76kg(0.6g/g) of 5% palladium on carbon to a 200 L autoclave, introduce hydrogen until the pressure of the system is 0.9±0.05 MPa, control the temperature

of the system at 30±5°C and the pressure at 0.9±0.05 MPa, react for 24 hours, filter the system, and regulate the pH to 12±0.5 to obtain a methanol solution containing 2.5kg of acetylamino-7,8-dihydropteridine

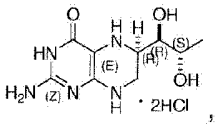


which is used directly in the next step;

Step 10: add 1.5 kg (0.6 g/g) of Raney nickel to the methanol solution containing 2.5kg of acetylamino-7,8-dihydropteridine

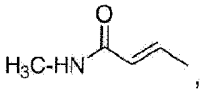


obtained in Step 9, introduce hydrogen until the pressure of the system is 0.9±0.05MPa, control the temperature of the system at 30±5°C and the pressure at 0.9±0.05MPa, react for 84 hours, after reacting thoroughly, perform quenching in 16.2kg(10eq) of dilute hydrochloric acid having a concentration of 20%, and perform suction filtration and drying to the system to obtain a target product, i.e. a crude product of sapropterin dihydrochloride



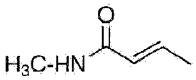
recrystallize and purify the crude product by 62.5L (25ml/g) of acetone at 40±5°C to obtain 1.31 kg of a pure product, with a yield of 47%, a purity of 98.1% and an enantiomeric excess of 98.9%.

[0015] Embodiment 3: main raw material:

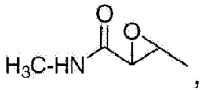


R=-CH_3 and X=NH

Step 1: add 495L(5g/ml) of ethanol, and 99kg(1 eq) of crotonyl methanamine



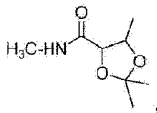
to a 2000L reaction kettle, increase the system temperature to 35±5°C, add 180.2kg(1eq) of a tert-butyl hydroperoxide toluene solution having a concentration of 50%, react for 2 hours while preserving the temperature, add 400kg(1 eq) of a sodium hydroxide solution having a concentration of 10% to the system, react for 3 hours while preserving the temperature, perform extraction and concentration to obtain 70.2kg of 2,3 epoxy - butyryl methylamine



with a yield of 61%;

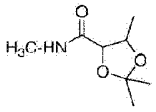
Step 2: in the presence of 106kg of (3eq) acetone, add 2.6kg(0.1 eq) of lithium chloride to a 1000L reaction kettle, control the temperature at 10±5°C, add 70.2kg(1.0eq) of 2,3 epoxy -

butyryl methylamine, react for 5 hours while preserving the temperature, add 610kg of a potassium bicarbonate (0.5eq) solution having a concentration of 5% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 81.3kg of 2,3-acetonide-alkylformamide

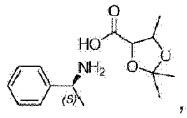


with a yield of 77%;

Step 3: add 243.9 L-(3ml/g) of ethanol, and 81.3kg(1 eq) of 2,3-acetonide-alkylformamide

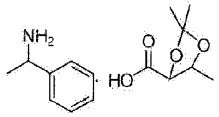


to a 1000L reaction kettle, increase the temperature to 250±5°C, add 4.23kg(0.5eq) of pure water and 47kg(0.5eq) of a sodium hydroxide solution having a concentration of 20%, react for 3 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 122.6L (2ml/g) of ethanol, add 56.9kg(1 eq) of L-α-phenylethylamine, preserve the temperature at 15±5°C for 3 hours, and perform centrifugation and drying to obtain 32.3kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-phenylpropylamino carboxylate

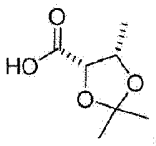


with a yield of 24.5%;

Step 4: add 30L(3ml/g) of 1,4-dioxane, 10kg (1eq) of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-phenylpropylamino carboxylate

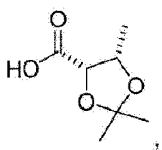


to a 72L reaction bottle, then add a dilute phosphoric acid aqueous solution having a concentration of 5% to the system to regulate the pH at 1±0.5, control the temperature at -10±5°C, react for 1 hour, perform liquid separation to obtain an organic phase, add 3.3kg of (0.8eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 5.2kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid



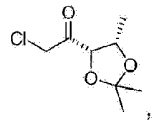
with a yield of 91%;

Step 5: add 26 L (5 ml/g) of 1,4-dioxane, 5.2 kg (1 eq) of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid



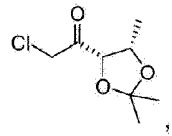
and 3.7kg(1 eq) of N,N-diisopropylethylamine to a 72L reaction bottle, reduce the temperature

to -30±5°C, add 3.1 kg(1 eq) of methyl chloroformate, react for 1 hour while preserving the temperature, introduce a diazomethane gas for 1 hour, add 2kg (1eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 1 hour, add potassium bicarbonate to regulate the pH value to 7±0.5, and perform extraction, liquid separation and concentration to obtain 5kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

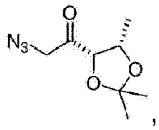


with a yield of 81%;

Step 6: add 25L(5ml/g) of methanol, 5kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

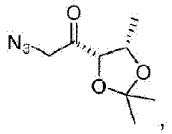


1.7 kg (1 eq) of sodium azide, and 0.22 kg (0.05eq) of potassium iodide to a 72 L bottle, after react the system for 20 hours while preserving the temperature at 15±5°C, perform filtering and concentration to obtain a methanol solution containing 4.5kg of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

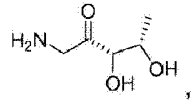


with a yield of 87%;

Step 7: add 22.5 L (5 ml/g) of methyl tert-butyl ether and 0.3 kg (0.05g/g) of 10% palladium on carbon to a 100L reaction kettle, introduce hydrogen until the system pressure is 0.4±0.1 MPa, regulate the pH of the system to 4±0.5 with benzenesulfonic acid, add the methanol solution containing 4.5kg (1 eq) of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

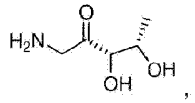


preserve the temperature at 10±5°C, react for 5 hours, perform suction filtration and concentration to obtain a filtrate containing 2.6kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone a yield of 86%;



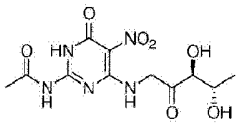
with

Step 8: add 21 L (5 ml/g) of ethanol, 4.2L(1ml/g) of pure water, 0.1 kg of (0.05eq) sodium iodide, 3.2kg(1 eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 1.83kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone



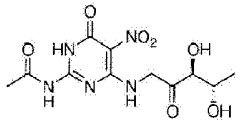
and 4.4kg(3eq) of sodium carbonate to a 50L reaction bottle, react the system for 4 hours

while preserving the temperature at 30±5°C, then add a sodium dihydrogen phosphate-disodium hydrogen phosphate aqueous solution to regulate the pH of the system to 6±0.5; and filter the system to obtain 1.9kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

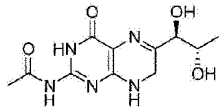


with a yield of 42%;

Step 9: add 3.8kg(1 eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

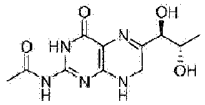


76L(20ml/g) of ethanol and 0.2kg(0.05g/g) of 20% palladium on carbon to a 100L autoclave, introduce hydrogen until the system pressure is 0.4±0.05MPa, control the temperature of the system at 15±5°C and the pressure at 0.4±0.05MPa, react for 18 hours, filter the system, and regulate the pH to 11±0.5 to obtain of an ethanol solution containing 3.25kg of acetylamino-7,8-dihydropteridine

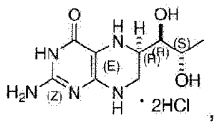


which is used directly in the next step;

Step 10: add 0.16kg(0.05g/g) of platinum dioxide in the presence of the ethanol solution containing 3.25kg of acetylamino-7,8-dihydropteridine

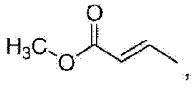


obtained in Step 9, introduce hydrogen until the system pressure is 0.4±0.05MPa, control the temperature of the system at 10±5°C and the pressure at 0.4±0.05MPa, react for 72 hours, after reacting thoroughly, perform quenching in 12.6kg(3eq) of dilute hydrochloric acid having a concentration of 10%, and perform suction filtration and drying to the system to obtain a target product, i.e. a crude product of sapropterin dihydrochloride



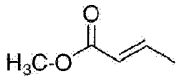
recrystallize and purify the crude product by 16.3L (5ml/g) of isopropanol at 0±5°C, to obtain 1.52kg of a pure product, with a yield of 42%, a purity of 98.0% and an enantiomeric excess of 98.7%.

[0016] Embodiment 4: main raw material:

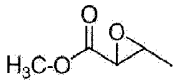


R=-CH_3 and X=O

Step 1: add 900 L (15 g/ml) of isopropanol, and 60 kg (1 eq) of methyl crotonate



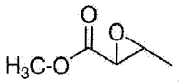
to a 2000 L reaction kettle, increase the system temperature to 45+5°C, add 178kg(2.5eq) of N-bromobutanimide, react for 3.5 hours while preserving the temperature, add 420kg(2.5eq) of a potassium hydroxide solution having a concentration of 20% to the system, react for 3.5 hours while preserving the temperature, perform extraction and concentration to obtain 42.6kg of 2,3 epoxy-methyl butyrate



,

with a yield of 61.2%;

Step 2: in the presence of 256 kg of (12eq) acetone, add 40 kg (0.8eq) of zinc chloride to a 2000 L reaction kettle, control the temperature at 25±5°C, add 42.6kg(1.0eq) of 2,3 epoxy-methyl butyrate



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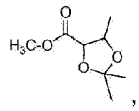
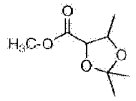
react for 9 hours while preserving the temperature, add 1408kg of a potassium carbonate (2.5eq) solution having a concentration of 9% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 49.8kg of 2,3-acetonide-methyl butyrate



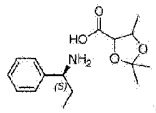
,

with a yield of 78%;

Step 3: add 398(8ml/g) of methanol, and 49.8kg(1 eq) of 2,3-acetonide-methyl butyrate



to a 1000L reaction kettle, increase the temperature to 35±5°C, add 9.3kg(1.8eq) of pure water and 144.5kg(1.8eq) of a potassium hydroxide aqueous solution having a concentration of 20%, react for 6.5 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 398L (8ml/g) of methanol, add 154.7kg(4eq) of L-α-amphetamine, preserve the temperature at 25±5°C for 4.5 hours, and perform centrifugation and drying to obtain 21.1 kg of 1-phenylpropan-1-amine (4S,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate



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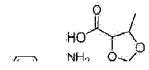
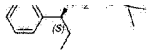
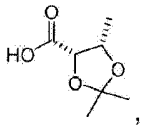
with a yield of 25%;

Step 4: add 48 L (8 ml/g) of methyl tert-butyl ether, 6kg (1 eq) of 1-phenylpropan-1-amine (4S,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate



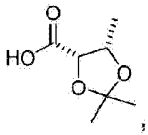


to a 72L reaction bottle, then add a dilute hydrochloric acid aqueous solution having a concentration of 9% to the system to regulate the pH at 2.5±0.5, control the temperature at -5±5°C, react for 1 hour, perform liquid separation to obtain an organic phase, add 6.6kg of (2.5eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 3.0kg of 1,3-dioxolan-4-carboxylic acid

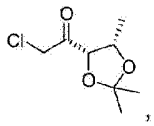


with a yield of 92%;

Step 5: add 36L(12 ml/g) of tetrahydrofuran, 3.0kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid

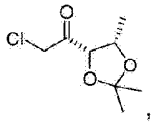


and 9.7kg(4eq) of N,N-diisopropylethylamine to a 72L reaction bottle, reduce the temperature to -25±5°C, add 4.4kg(2.5eq) of methyl chloroformate, react for 1.5 hours while preserving the temperature, introduce a diazomethane gas for 1.5 hours, add 15.3kg (4.5eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 1.5 hours, add triethylamine to regulate the pH value to 8.5±0.5, and perform extraction, liquid separation and concentration to obtain 3.0kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

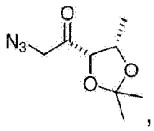


with a yield of 83%;

Step 6: add 36L(12ml/g) of acetone, 3kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane



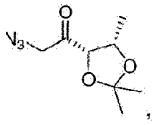
3kg(3eq) of sodium azide, and 1.5kg (0.6eq) of sodium iodide to a 72L bottle, react the system for 27 hours while preserving the temperature at 32±5°C, perform filtering and concentration to obtain an acetone solution containing 2.8kg of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane



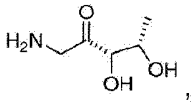
with a yield of 91%;

Step 7: add 33.7L (12ml/g) of 2-methyltetrahydrofuran, 8.6kg(2.0eq) of triphenylphosphine, and 0.5kg(2.0eq) of water to a 72L reaction kettle, regulate the pH of the system to 3±0.5 with acetic acid, add the acetone solution containing 2.8kg of (4S,5S)-2,2,5-trimethyl-5-(2-

azidoacetyl)-1,3-dioxolane

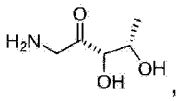


preserve the temperature at 25±5°C, react for 8.5 hours, perform suction filtration and concentration to obtain a filtrate containing 1.6kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

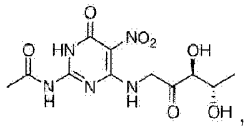


with a yield of 87.5%;

Step 8: add 19.7 L(12 ml/g) of methanol, 6.4L(4ml/g) of pure water, 0.8kg of (0.4eq) of sodium iodide, 4.0kg(1.4eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 1.6kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

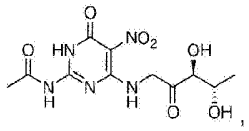


and 8.7kg(7eq) of potassium bicarbonate to a 50L reaction bottle, react the system for 7 hours while preserving the temperature at 70±5°C, then add a sodium dihydrogen phosphate-disodium hydrogen phosphate aqueous solution to regulate the pH of the system to 7.5±0.5; and filter the system to obtain 1.7kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

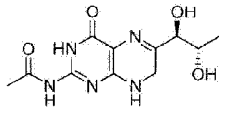


with a yield of 43%;

Step 9: add 1.7kg(1 eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

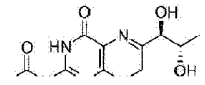


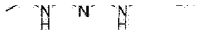
78.7L(45ml/g) of methanol and 0.9kg(0.5g/g) of 5% palladium on carbon to a 100L autoclave, introduce hydrogen until the reaction system pressure is 0.8±0.05MPa, control the temperature of the system at 25±5°C and the pressure at 0.8±0.05MPa, react for 22 hours, filter the system, and regulate the pH to 11±0.5 to obtain a methanol solution containing 1.5kg of acetylamino-7,8-dihydropteridine



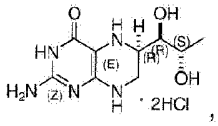
which is used directly in the next step;

Step 10: add 0.7kg(0.05g/g) of 5% palladium on carbon in the presence of the methanol solution containing 1.5kg of acetylamino-7,8-dihydropteridine



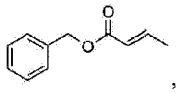


obtained in Step 9, introduce hydrogen until the pressure of the reaction kettle is 0.8±0.05MPa, control the temperature of the system at 25±5°C and the pressure at 0.8±0.05MPa, react for 82 hours, after reacting thoroughly, perform quenching in 31.9kg(9eq) of dilute hydrochloric acid having a concentration of 15%, and perform suction filtration and drying to the system to obtain a target product, i.e. a crude product of sapropterin dihydrochloride

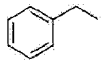


recrystallize and purify the crude product by 29L (20ml/g) of methanol at 35±5°C to obtain 0.8 kg of a pure product, with a yield of 45%, a purity of 98.3% and an enantiomeric excess of 99.1%.

[0017] Embodiment 5: main raw material:

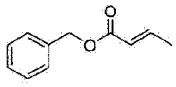


R=

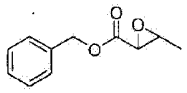


and X=O

Step 1: add 780L(12g/ml) of ethanol, and 65kg(1eq) of benzyl crotonate

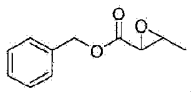


to a 2000L reaction kettle, increase the system temperature to 42±5°C, add 127.3kg(2eq) of meta-chloroperoxybenzoic acid, react for 3 hours while preserving the temperature, add 147.6kg(2eq) of a sodium hydroxide solution having a concentration of 20% to the system, react for 3.2 hours while preserving the temperature, perform extraction and concentration to obtain 44kg of 2,3-epoxy-benzyl butyrate

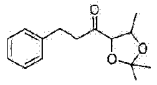


with a yield of 62%;

Step 2: in the presence of 132.8kg of (10eq) acetone, add 5.8kg(0.6eq) of lithium chloride to a 1000L reaction kettle, control the temperature at 22±5°C, add 44kg(1.0eq) of 2,3-epoxy-benzyl butyrate

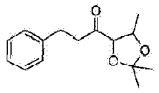


react for 7 hours while preserving the temperature, add 343kg of a potassium dicarbonate (1.5eq) solution having a concentration of 10% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 44kg of 2,3-acetonide-benzyl butyrate

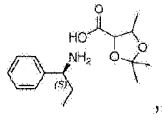


with a yield of 77.5%;

Step 3: add 352(8ml/g) of ethanol, and 44kg(1 eq) of 2,3-acetonide-benzyl butyrate

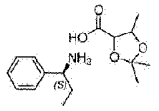


to a 1000L reaction kettle, increase the temperature to 37±5°C, add 4.8kg(1.5eq) of pure water and 53.2kg(1.5eq) of a sodium hydroxide aqueous solution having a concentration of 20%, react for 6 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 352L (8ml/g) of ethanol, add 71.9kg(3eq) of L-α-amphetamine, preserve the temperature at 22±5°C for 4 hours, and perform centrifugation and drying to obtain 13.2kg of 1-phenylpropan-1-amine (4S,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate

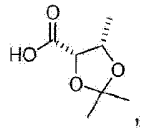


with a yield of 25.3%;

Step 4: add 48L(6ml/g) of 1,4-dioxane, 8kg (1 eq) of 1-phenylpropan-1-amine (4S,5S)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate

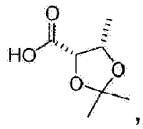


to a 72 L reaction bottle, then add a dilute sulphuric acid aqueous solution having a concentration of 10% to the system to regulate the pH at 2.5±0.5, control the temperature at -5±5°C, react for 1 hour, perform liquid separation to obtain an organic phase, add 7.0kg of (2.0eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 4.1 kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid

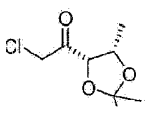


with a yield of 93.5%;

Step 5: add 49L(12 ml/g) of 2-methyltetrahydrofuran, 4.1kg of 1,3-dioxolan-4-carboxylic acid



and 13.1 kg(4eq) of N,N-diisopropylethylamine to a 100L reaction bottle, reduce the temperature to -22±5°C, add 5.5kg(2.0eq) of ethyl chloroformate, react for 1.8 hours while preserving the temperature, introduce a diazomethane gas for 1.8 hours, add 18.5kg (4.5eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 1.8 hours, add potassium bicarbonate to regulate the pH value to 8.5±0.5, and perform extraction, liquid separation and concentration to obtain 4.1 kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane



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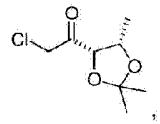
with a yield of 83.7%;

Step 6: add 49L(12ml/g) of acetone, 4.1 kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane



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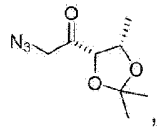
3.4kg(2.5eq) of sodium azide, and 1.8kg (0.5eq) of potassium iodide to a 72L bottle, react the system for 26 hours while preserving the temperature at 34±5°C, perform filtering and concentration to obtain an acetone solution containing 3.9kg of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane



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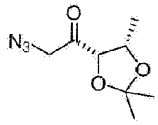
with a yield of 91.5%;

Step 7: add 46.4L (12ml/g) of methyl tert-butyl ether and 1.2kg(0.3g/g) of Raney nickel to a 100L reaction kettle, introduce hydrogen until the system pressure is 0.8±0.1 MPa, regulate the pH of the system to 3±0.5 with concentrated sulfuric acid, add an acetonitrile solution containing 3.9kg(1 eq) of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane



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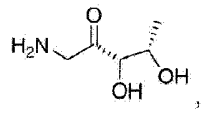
react at 27±5°C for 8.5 hours, perform suction filtration and concentration to obtain 2.3kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone



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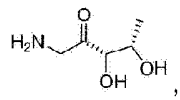
with a yield of 89%;

Step 8: add 23L(10ml/g) of propanol, 6.9L(3ml/g) of pure water, 0.9kg of (0.3eq) of potassium iodide, 4.8kg(1.2eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 2.3kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone



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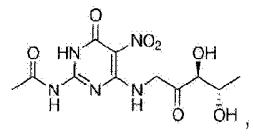
and 10.5kg(6eq) of diisopropylamine to a 50L reaction bottle, react the system for 7 hours while preserving the temperature at 72±5°C, then add a potassium dihydrogen phosphate-dipotassium phosphate aqueous solution to regulate the pH of the system to 7.5±0.5; and filter the system to obtain 2.5kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one



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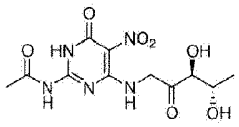
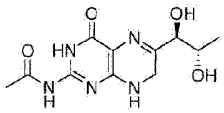
with a yield of 44%;

Step 9: add 1.25kg(1 eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

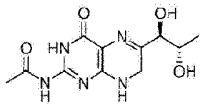


50L(40ml/g) of ethanol and 0.5kg(0.4g/g) of 10% palladium on carbon to a 100L autoclave, introduce hydrogen until the reaction system pressure is 0.8±0.05MPa, control the temperature of the system at 27±5°C and the pressure at 0.8±0.05MPa, react for 24 hours, filter the system, and regulate the pH to 11±0.5 to obtain an ethanol solution containing 1.1kg of acetylamino-7,8-dihydropteridine

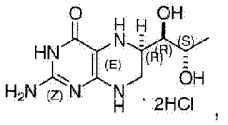


which is used directly in the next step;

Step 10: add 0.44kg(0.4g/g) of 10% palladium on carbon in the presence of the ethanol solution containing 1.1 kg of acetylamino-7,8-dihydropteridine

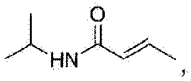


obtained in Step 9, introduce hydrogen until the pressure of the reaction kettle is 0.8±0.05MPa, control the temperature of the system at 25±5°C and the pressure at 0.8±0.05MPa, react for 80 hours, after reacting thoroughly, perform quenching in 20kg(8eq) of dilute hydrochloric acid having a concentration of 15%, and perform suction filtration and drying to the system to obtain a target product, i.e. a crude product of sapropterin dihydrochloride



recrystallize and purify the crude product by 21.4L (20ml/g) of ethanol at 35±5°C to obtain 0.4 kg of a pure product, with a yield of 46.2%, a purity of 98.5% and an enantiomeric excess of 99.2%.

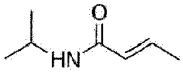
[0018] Embodiment 6: main raw material:



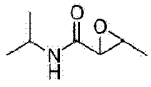
R=

and X=N

Step 1: add 510L(6g/ml) of methanol, and 85kg(1eq) of (E)-N-isopropylbut-2-enamide



to a 2000 L reaction kettle, increase the system temperature to 37±5°C, add 120.5kg(1 eq) of tert-butyl hydroperoxide toluene solution having a concentration of 50%, react for 2.5 hours while preserving the temperature, add 133.7kg(1 eq) of a sodium hydroxide solution having a concentration of 20% to the system, react for 3.5 hours while preserving the temperature, perform extraction and concentration to obtain 59kg of N-isopropyl-3-methyloxirane-2-carboxamide



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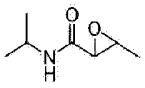
with a yield of 61.7%;

Step 2: in the presence of 119.8kg of (5eq) acetone, add 9.3kg(0.1 eq) of zinc bromide to a 1000L reaction kettle, control the temperature at 15±5°C, add 59kg(1.0eq) of N-isopropyl-3-methyloxirane-2-carboxamide



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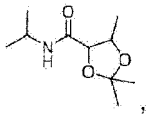
react for 6 hours while preserving the temperature, add 173kg of a sodium dicarbonate (0.5eq) solution having a concentration of 10% to the system, and perform liquid separation, extraction, and concentration in the system to obtain 64.7kg of N-isopropyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxamide



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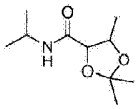
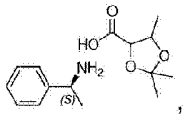
with a yield of 78%;

Step 3: add 259(4ml/g) of tetrahydrofuran, and 64.7kg(1 eq) of N-isopropyl-2,2,5-trimethyl-1,3-dioxolane-4-carboxamide



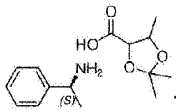
to a 1000 L reaction kettle, increase the temperature to 27±5°C, add 2.9kg(0.5eq) of pure water and 29.9kg(0.5eq) of a methanol solution of sodium methoxide having a concentration of 29%, react for 4 hours while preserving the temperature, perform centrifugation, dissolve a filter cake in 194L (3ml/g) of tetrahydrofuran, add 39kg(1 eq) of L-α-phenylethylamine, preserve the temperature at 18±5°C for 3.5 hours, and perform centrifugation and drying to obtain 22.4kg of 1-phenylethanamine 2,2,5-trimethyl-1,3-dioxolane-4-carboxylate



,

with a yield of 24.7%;

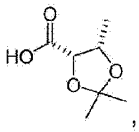
Step 4: add 30L(3ml/g) of 2-methyltetrahydrofuran, 10kg (1eq) of 1-phenyltehanamine -2,2,5-trimethyl-1,3-dioxolane-4-carboxylat



.

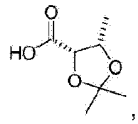
to a 72L reaction bottle, then add a dilute phosphoric acid aqueous solution having a

concentration of 10% to the system to regulate the pH at 1.5±0.5, control the temperature at -5±5°C, react for 1 hour, perform liquid separation to obtain an organic phase, add 3.7kg of (0.8eq) N,N-diisopropylethylamine to the organic phase, and concentrate the system to obtain 5.3kg of (4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-methanoic acid

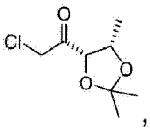


with a yield of 92.5%;

Step 5: add 42L(8 ml/g) of 1,4-dioxane, 5.3kg of 1,3-dioxolan-4-carboxylic acid

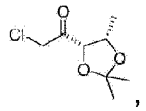


and 8.5kg(2eq) of N,N-diisopropylethylamine to a 100L reaction bottle, reduce the temperature to -10±5°C, add 4kg(21.0eq) of propyl chloroformate, react for 2 hours while preserving the temperature, introduce a diazomethane gas for 2 hours, add 12kg (2eq) of a hydrochloride ethanol solution having a concentration of 20%, react for 2 hours, add sodium hydroxide to regulate the pH value to 7.5±0.5, and perform extraction, liquid separation and concentration to obtain 5.1 kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

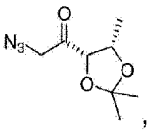


with a yield of 81%;

Step 6: add 41 L(8ml/g) of tetrahydrofuran, 5.1kg of (4S,5S)-2,2,5-trimethyl-5-chloroacetyl-1,3-dioxolane

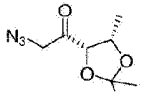


3.1 kg(1 eq) of azidotrimethylsilane, and 0.5kg (0.1 eq) of sodium iodide to a 72L bottle, react the system for 30 hours while preserving the temperature at 12±5°C, perform filtering and concentration to obtain an acetone solution containing 4.6kg of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

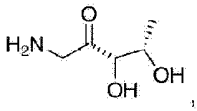


with a yield of 87.5%;

Step 7: add 28L (6ml/g) of 1,4-dioxane and 0.23kg(0.05g/g) of 10% palladium on carbon to a 50L reaction kettle, introduce hydrogen until the system pressure is 0.8±0.1MPa, regulate the pH of the system to 3±0.5 with acetic acid, add an acetonitrile solution containing 4.6kg(1 eq) of (4S,5S)-2,2,5-trimethyl-5-(2-azidoacetyl)-1,3-dioxolane

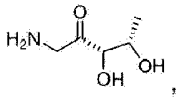


react at 27±5°C for 8.5 hours, perform suction filtration and concentration to obtain 2.7 kg of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

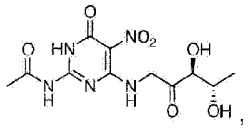


with a yield of 87.7%;

Step 8: add 16.3 L (6 ml/g) of isopropanol, 2.7 L (1 g/g) of pure water, 0.4kg of (0.1 eq) of sodium iodide, 4.8kg(1.0eq) of compound A (2-amino-6-chloro-5-nitro-3H-pyrimidin-4-one), 2.7kg(1eq) of (3S,4S)-1-amino-3,4-dihydroxy-2-pentanone

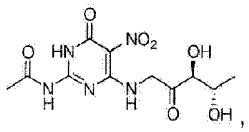


and 8.7kg(4eq) of sodium carbonate to a 50L reaction bottle, react the system for 7 hours while preserving the temperature at 45±5°C, then add an ammonium formate-ammonia aqueous solution to regulate the pH of the system to 6.5±0.5; and filter the system to obtain 2.85kg of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

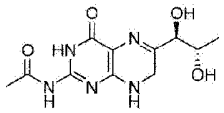


with a yield of 42.5%;

Step 9: add 2kg(1 eq) of 2-acetylamino-5-nitro-6-((3S,4S)-3,3-dihydroxy-2-oxo-pentylamino)-pyrimidin-4-one

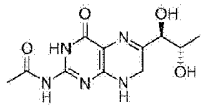


60L(30ml/g) of ethanol and 0.2kg(0.1g/g) of platinum dioxide to a 100L autoclave, introduce hydrogen until the reaction system pressure is 0.6±0.05MPa, control the temperature of the system at 20±5°C and the pressure at 0.6±0.05MPa, react for 20 hours, filter the system, and regulate the pH to 11±0.5 to obtain an ethanol solution containing 1.7kg of acetylamino-7,8-dihydropteridine



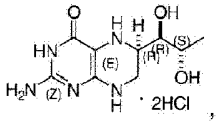
which is used directly in the next step;

Step 10: add 0.2kg(0.1g/g) of platinum dioxide in the presence of the ethanol solution containing 1.7kg of acetylamino-7,8-dihydropteridine



obtained in Step 9, introduce hydrogen until the pressure of the reaction kettle is 0.6±0.05MPa, control the temperature of the system at 15±5°C and the pressure at 0.6±0.05MPa, react for 75 hours, after reacting thoroughly, perform quenching in 30kg(5eq) of dilute hydrochloric acid having a concentration of 10%, and perform suction filtration and drying to the system to obtain

a target product, i.e. a crude product of sapropterin dihydrochloride



recrystallize and purify the crude product by 17L (10ml/g) of butanone at 15±5°C to obtain 0.6 kg of a pure product, with a yield of 43%, a purity of 98.4% and an enantiomeric excess of 98.9%.

[0019] Thus, it can be seen that synthesis of a sapropterin dihydrochloride compound disclosed in a method of the present invention can obtain a target product with a high purity, a high enantiomeric excess, and a high yield. The synthesis method uses readily-available raw materials, significantly reduces a synthesis route of sapropterin dihydrochloride. The technological conditions are stable, and there is less pollution in the whole operation process, hence providing an effective scheme for mass industrial production of sapropterin dihydrochloride.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO2009047902A1 [0004]
- WO2005049614A2 [0004]
- JP2575781B [0004]

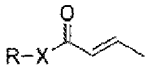
Non-patent literature cited in the description

- **E.L.PATTERSON et al.**J.Am.Chem.Soc., 1956, vol. 78, 5868- [0003]
- **MATSUURA et al.**Bull.Chem.Soc.Jpn., 1975, vol. 48, 3767- [0003]
- **MATSUURA et al.**Chemistry of Organic Synthesis,Ml/g, 1988, vol. 46, 6570- [0003]

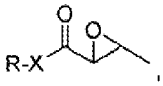
P A T E N T K R A V

1. Fremgangsmåde til syntetisering af sapropterindihydrochlorid, **kendetegnet ved, at** den omfatter følgende trin:

trin 1: en forbindelse 1 med formlen

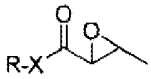


underkastes epoxydering for at frembringe en forbindelse 2 med formlen

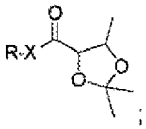


hvor X=NH eller O, R=C1-C6 alkan eller benzyl;

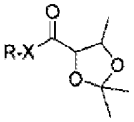
trin 2: i nærvær af acetone, en Lewis-syre, en uorganisk basevæske reagerer forbindelsen 2 med formlen



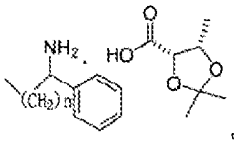
for at frembringe en forbindelse 3 med formlen



trin 3: forbindelsen 3 med formlen

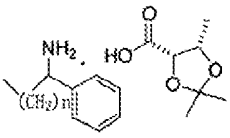


reagerer i en alkalisk opløsning, et polært opløsningsmiddel anvendes til at opløse en filterkage opnået ved centrifugering, derefter tilsættes en opløsningsreagens for at gennemføre opløsning for at opnå en forbindelse 4 med formlen

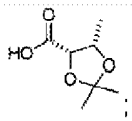


hvor n=0,1;

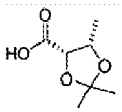
trin 4: at opløse forbindelsen 4 med formlen



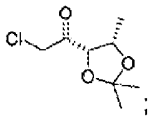
i et etheropløsningsmiddel og at gennemføre separation under sure betingelser for at opnå en organisk fase og at tilsætte N,N-diisopropyl-ethylamin til den organiske fase for at opnå en forbindelse 5 med formlen



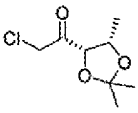
trin 5: at anvende forbindelsen 5 med formlen



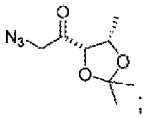
som et råmateriale til at syntetisere en forbindelse 6 med formlen



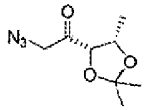
trin 6: at reagere forbindelsen 6 med formlen



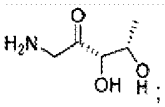
med en trinitrid for at frembringe en forbindelse 7 med formlen



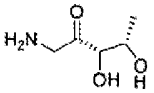
trin 7: at underkaste forbindelsen 7 med formlen



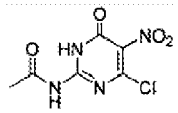
hydrogenering for at opnå en forbindelse 8 med formlen

 ;

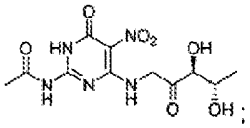
trin 8: at reagere forbindelsen 8 med formlen



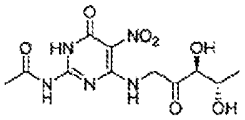
og en forbindelse A med formlen



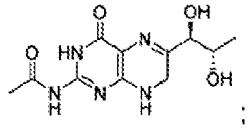
for at frembringe en forbindelse 9 med formlen

 ;

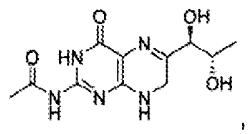
trin 9: at underkaste forbindelsen 9 med formlen



cyclisering for at opnå en forbindelse 10 med formlen

 ;

trin 10: at tilsætte en katalysator til forbindelsen 10 med formlen

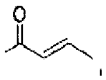
 ,

at indføre hydrogen for at gennemføre en reaktion og derefter at gennemføre

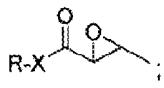
køling i saltsyre med en koncentration på 10% til 20% for at opnå sapropterin-dihydrochlorid.

2. Syntetiseringsfremgangsmåde ifølge krav 1, **kendetegnet ved, at** den omfatter følgende trin:

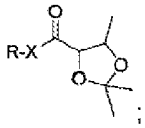
trin 1: i nærvær af et polært opløsningsmiddel at tilsætte forbindelsen 1 med formlen R-X



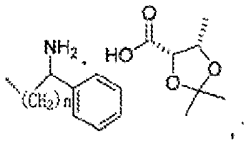
at øge systemtemperaturen til 35°C til 50°C, at tilsætte et oxidationsmiddel, at reagere i 2 til 5 timer, mens temperaturen opretholdes, derefter at tilsætte en vandig opløsning af en stærk base med en koncentration på 10 vægt-% til 20 vægt-% til systemet, mens temperaturen opretholdes, at reagere systemet i 3 til 4 timer efter tilsætning af den vandige opløsning af en stærk base og at gennemføre ekstraktion og koncentration for at opnå forbindelsen 2 med formlen



trin 2: at tilsætte en Lewis-syre i nærvær af acetone, at styre temperaturen ved 10°C til 30°C, at tilsætte forbindelsen 2, at reagere i 5 til 10 timer, mens temperaturen opretholdes, at tilsætte en uorganisk baseopløsning med en koncentration på 5 vægt-% til 10 vægt-% til systemet og at gennemføre væskeseparation, ekstraktion og koncentration på systemet for at opnå forbindelsen 3 med formlen

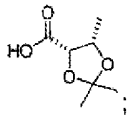


trin 3: at tilsætte forbindelsen 3 i nærvær af et polært opløsningsmiddel, at øge temperaturen til 25°C til 40°C, at tilsætte rent vand og en alkalisk opløsning, at reagere i 3 til 8 timer, mens temperaturen opretholdes, at gennemføre centrifugering, at opløse en filterkage i et polært opløsningsmiddel, som er det samme som det polære opløsningsmiddel anvendt i reaktionen, at tilsætte en opløsningsreagens, at opretholde temperaturen ved 15°C til 30°C i 3 til 5 timer, at gennemføre centrifugering og at tørre for at opnå forbindelsen 4 med formlen



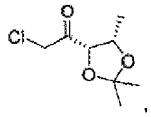
hvor n=0,1;

trin 4: at tilsætte forbindelsen 4 i nærvær af et etheropløsningsmiddel, derefter at tilsætte en vandig uorganisk syreopløsning med en koncentration på 5% til 10% til systemet for at regulere pH til 1 til 3, at styre temperaturen ved -10°C til 10°C, at opretholde temperaturen i 1 time, at gennemføre væskeseparation for at opnå en organisk fase, at tilsætte N,N-diisopropylethylamin til den organiske fase og at koncentrere systemet for at opnå forbindelsen 5 med formlen

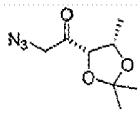


trin 5: at tilsætte forbindelsen 5 og N,N-diisopropylethylamin i nærvær af et etheropløsningsmiddel, at sænke temperaturen til -30°C til 0°C, at tilsætte et chloroformiat, at reagere i 1 til 2 timer, mens temperaturen opretholdes, at indføre en diazomethangas i 1 til 2 timer, at tilsætte en hydrochlorid-ethanolopløsning, at reagere i 1 til 2 timer, at tilsætte en alkalisk reagens for

at regulere pH-værdien til 7 til 9, at gennemføre ekstraktion, væske-separation og koncentration for at opnå forbindelsen 6 med formlen

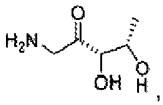


trin 6: at tilsætte forbindelsen 6, en trinitrid og en katalysator i nærvær af et polært opløsningsmiddel, at reagere systemet ved 15°C til 40°C i 20 til 30 timer, mens temperaturen opretholdes, derefter at gennemføre filtrering og koncentration for at opnå en opløsning af forbindelsen 7 med formlen



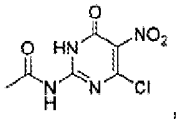
der anvendes direkte i det næste trin;

trin 7: at tilsætte triphenylphosphin og vand eller palladium på carbon og hydrogen eller Raney-nikkel og hydrogen i nærvær af et etheropløsnings-middel, at regulere systemets pH til 1 til 4 med en syrereagens, at tilsætte en opløsning af forbindelsen 7, at opretholde temperaturen ved 10°C til 30°C, at reagere i 5 til 10 timer, at gennemføre vakuumfiltrering og koncentration for at opnå et filtrat, der indeholder forbindelsen 8 med formlen



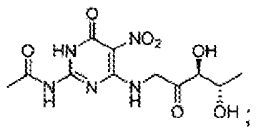
hvor filtratet anvendes direkte i det næste trin, eller et faststof af forbindelsen 8, der separeres fra filtratet til anvendelse i det næste trin;

trin 8: at tilsætte en katalysator, forbindelsen A med formlen

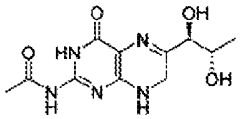


forbindelsen 8 og en alkalisk reagens i nærvær af et alkoholholdigt opløs-ningsmiddel og rent vand, at reagere systemet ved 30°C til 80°C i 4 til 8 timer, mens temperaturen opretholdes, at tilsætte en bufferopløsning for at regulere

systemets pH til 6 til 8 og at filtrere systemet for at opnå forbindelsen 9 med formlen



trin 9: at tilsætte en katalysator i nærvær af forbindelsen 9 og et polært opløsningsmiddel, at indføre hydrogen, indtil trykket i systemet er 0,4 til 0,9MPa, at styre temperaturen i systemet ved 15°C til 30°C og tryk ved 0,4 til 0,9MPa, at reagere i 18 til 24 timer, at filtrere systemet og at regulere systemets pH til 11 til 12 med en alkalisk reagens for at opnå en opløsning af forbindelsen 10 med formlen



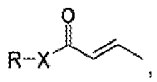
der skal anvendes direkte i det næste trin;

trin 10: at tilsætte en katalysator i nærvær af opløsningen af forbindelsen 10 opnået i trin 9, at indføre hydrogen, indtil trykket i systemet er 0,4 til 0,9MPa, at styre temperaturen i systemet ved 10°C til 30°C, at styre trykket ved 0,4 til 0,9MPa, at reagere i 72 til 84 timer, at gennemføre køling i fortyndet saltsyre med en koncentration på 10% til 20% efter grundig reaktion og at gennemføre vakuumfiltrering og tørring på systemet for at opnå et sapropterin-dihydrochloridråprodukt.

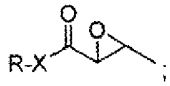
3. Syntetiseringsfremgangsmåde ifølge krav 2, **kendetegnet ved, at** trin 10 endvidere omfatter: at krystallisere og rense sapropterindihydrochloridråproduktet med et alkoholholdigt opløsningsmiddel eller et ketonopløsningsmiddel ved 0°C til 40°C for at opnå et rent sapropterindihydrochloridprodukt.

4. Syntetiseringsfremgangsmåde ifølge krav 1, **kendetegnet ved, at** den omfatter følgende trin:

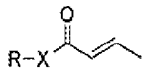
trin 1: i nærvær af et polært opløsningsmiddel at tilsætte forbindelsen 1 med formlen



hvor X=NH eller O, R=C1 til C6 alkan eller benzyl, at øge systemets temperatur til 35°C til 50°C, at tilsætte et oxidationsmiddel, at reagere i 2 til 5 timer, mens temperaturen opretholdes, derefter at tilsætte en vandig opløsning af en stærk base med en koncentration på 10% til 20% til systemet, mens temperaturen opretholdes, at reagere systemet i 3 til 4 timer efter tilsætning af den vandige opløsning af en stærk base og at gennemføre ekstraktion of koncentration for at opnå forbindelsen 2 med formlen

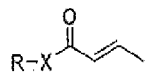


hvor forholdet mellem anvendelsesmængden af forbindelsen med formlen



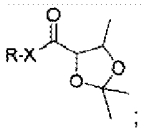
og den af det polære opløsningsmiddel er 1 g/5 to 20 ml, hvor molforholdet mellem forbindelsen med formlen R-X

og oxidationsmidlet er 1:1 til 3, og molforholdet mellem forbindelsen med formlen



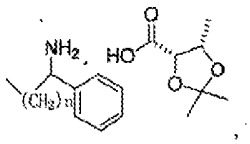
og den stærke base er 1:1 til 3;

trin 2: at tilsætte en Lewis-syre i nærvær af acetone, at styre temperaturen ved 10°C til 30°C, at tilsætte forbindelsen 2, at reagere i 5 til 10 timer, mens temperaturen opretholdes, at tilsætte en uorganisk baseopløsning med en koncentration på 5% til 10% til systemet og at gennemføre væskeseparation, ekstraktion og koncentration på systemet for at opnå forbindelsen 3 med formlen



hvor molforholdet mellem forbindelsen 2 og acetone er 1:3 til 15; molforholdet mellem forbindelsen 2 og Lewis-syren er 1: 0,1 til 1; og molforholdet mellem forbindelsen 2 og den uorganiske base er 1: 0,5 til 3;

trin 3: at tilsætte forbindelsen 3 i nærvær af et polært opløsningsmiddel, at øge temperaturen til 25°C til 40°C, at tilsætte rent vand og en alkalisk opløsning, at reagere i 3 til 8 timer, mens temperaturen opretholdes, at gennemføre centrifugering, at opløse en filterkage i et polært opløsningsmiddel, som er det samme som det polære opløsningsmiddel anvendt i reaktionen, at tilsætte en opløsningsreagens, at opretholde temperaturen ved 15°C til 30°C i 3 til 5 timer, at gennemføre centrifugering og at tørre for at opnå forbindelsen 4 med formlen

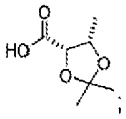


hvor n=0,1;

hvor forholdet mellem anvendelsesmængden af forbindelsen 3 og den af det polære opløsningsmiddel anvendt i reaktionen er 1 g/3 til 10 ml; molforholdet mellem forbindelsen 3 og rent vand er 1:0,5 til 3; molforholdet mellem forbindelsen 3 og en alkalisk substans i den alkaliske opløsning er 1:0,5 til 2; forholdet mellem anvendelsesmængden af forbindelsen 3 og den af det polære opløsningsmiddel til opløsning af filterkagen er 1 g/2 til 10 ml; og molforholdet mellem forbindelsen 3 og opløsningsreagensen er 1:1 til 5;

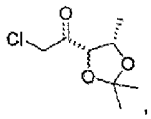
trin 4: at tilsætte forbindelsen 4 i nærvær af et etheropløsningsmiddel, derefter at tilsætte en vandig opløsning af en uorganisk syre med en koncentration på 5% til 10% til systemet for at regulere pH til 1 til 3, at styre temperaturen ved -10°C til 10°C, at gennemføre væskeseparation for at opnå en organisk fase, at tilsætte N,N-diisopropylethylamin til den organiske fase

og at koncentrere systemet for at opnå forbindelsen 5 med formlen



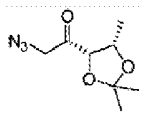
hvor forholdet mellem anvendelsesmængden af forbindelsen 4 og den af etheropløsningsmidlet er 1 g/3 til 10 ml, og molforholdet mellem forbindelsen 4 og N,N-diisopropylethylamin er 1:0,8 til 3;

trin 5: at tilsætte forbindelsen 5 og N,N-diisopropylethylamin i nærvær af et etheropløsningsmiddel, at sænke temperaturen til -30°C til 0°C, at tilsætte et chloroformiat, at reagere i 1 til 2 timer, mens temperaturen opretholdes, at indføre en diazomethangas i 1 til 2 timer, at tilsætte en hydrochloridethanol-opløsning, at reagere i 1 til 2 timer, at tilsætte en alkalisk reagens for at regulere pH-værdien til 7 til 9, at gennemføre ekstraktion, væskeseparation og koncentration for at opnå forbindelsen 6 med formlen



hvor forholdet mellem anvendelsesmængden af forbindelsen 5 og den af etheropløsningsmidlet er 1 g/5 til 15 ml; molforholdet mellem forbindelsen 5 og N,N-diisopropylethylamin er 1:1 til 5; molforholdet mellem forbindelsen 5 og chloroformiatet er 1:1 til 3; og molforholdet mellem forbindelsen 5 og hydrogenchlorid i hydrogenchlorid-ethanolopløsningen er 1:1 til 5;

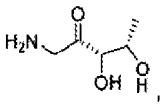
trin 6: at tilsætte forbindelsen 6, en trinitrid og en katalysator i nærvær af et polært opløsningsmiddel, at reagere systemet ved 15°C til 40°C i 20 til 30 timer, mens temperaturen opretholdes, derefter at gennemføre filtrering og koncentration for at opnå en opløsning af forbindelsen 7 med formlen



der anvendes direkte i det næste trin;
hvor forholdet mellem anvendelsesmængden af forbindelsen 6 og den af det

polære opløsningsmiddel er 1 g/5 til 15 ml; molforholdet mellem forbindelsen 6 og trinitriden er 1:1 til 4; og molforholdet mellem forbindelsen 6 og katalysatoren er 1:0,05 til 0,8;

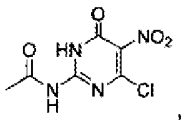
trin 7: at tilsætte triphenylphosphin og vand eller palladium på carbon og hydrogen eller Raney-nikkel og hydrogen i nærvær af et etheropløsningsmiddel, at regulere systemets pH til 1 til 4 med en syrereagens, at tilsætte en opløsning af forbindelsen 7, at opretholde temperaturen ved 10°C til 30°C, at reagere i 5 til 10 timer, at gennemføre vakuumfiltrering og koncentration for at opnå et filtrat, der indeholder forbindelsen 8 med formlen



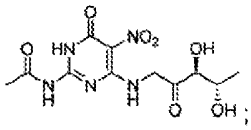
hvor filtratet anvendes direkte i det næste trin, eller et faststof af forbindelsen 8, der separeres fra filtratet til anvendelse i det næste trin;

hvor forholdet mellem anvendelsesmængden af forbindelsen 7 og den af etheropløsningsmidlet er 1 g /5 til 15 ml; molforholdet mellem forbindelsen 7 og triphenylphosphin er 1:0,1 til 3; forholdet mellem anvendelsesmængden af forbindelsen 7 og den af vand er 1:0,1 til 3; masseforholdet mellem forbindelsen 7 og 5% palladium på carbon eller 10% palladium på carbon eller Raney-nikkel er 1:0,05 til 0,6; hydrogenet indføres, indtil trykket i systemet er 0,4 til 0,9MPa;

trin 8: at tilsætte en katalysator, forbindelsen A med formlen

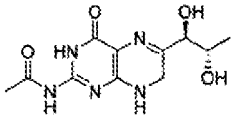


og en alkalisk reagens i nærvær af et alkoholholdigt opløsningsmiddel og rent vand, at reagere systemet ved 30°C til 80°C i 4 til 8 timer, mens temperaturen opretholdes, at tilsætte en bufferopløsning for at regulere systemets pH til 6 til 8, og at filtrere systemet for at opnå forbindelsen 9 med formlen



hvor forholdet mellem anvendelsesmængden af forbindelsen 8 og den af det alkoholholdige opløsningsmiddel er 1 g/5 til 15 ml; forholdet mellem anvendelsesmængden af forbindelsen 8 og den af rent vand er 1 g/1 til 5 ml; molforholdet mellem forbindelsen 8 og forbindelsen A er 1:1 til 1,5; molforholdet mellem forbindelse 8 og katalysatoren er 1:0,05 til 0,5; og molforholdet mellem forbindelsen 8 og den alkaliske reagens er 1:3 til 8;

trin 9: at tilsætte en katalysator i nærvær af forbindelsen 9 og et polært opløsningsmiddel, at indføre hydrogen, indtil trykket i systemet er 0,4 til 0,9MPa, at styre temperaturen i systemet ved 15°C til 30°C og trykket ved 0,4 til 0,9MPa, at reagere i 18 til 24 timer, at filtrere systemet og at regulere systemets pH til 11 til 12 med en alkalisk reagens for at opnå en opløsning af forbindelsen 10 med formlen



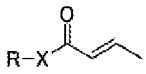
som skal anvendes direkte i det næste trin; hvor forholdet mellem anvendelsesmængden af forbindelsen 9 og den af det polære opløsningsmiddel er 1 g/20 til 50 ml, og masseforholdet mellem forbindelsen 9 og katalysatoren er 1:0,05 til 0,6;

trin 10: at tilsætte en katalysator i nærvær af opløsningen af forbindelsen 10 opnået i trin 9, at indføre hydrogen, indtil trykket i systemet er 0,4 til 0,9MPa, at styre temperaturen i systemet ved 10°C til 30°C, at styre trykket ved 0,4 til 0,9MPa, at reagere i 72 til 84 timer, at gennemføre køling i fortyndet saltsyre med en koncentration på 10% til 20% efter grundig reaktion og at gennemføre vakuumfiltrering og tørring på systemet for at opnå et sapropterindihydrochloridråprodukt og endvidere at krystallisere og rense

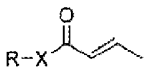
sapropterindihydrochloridråproduktet med et alkoholholdigt opløsningsmiddel eller et ketonopløsningsmiddel ved 0°C til 40°C for at opnå et rent sapropterindihydrochloridprodukt,

hvor masseforholdet mellem forbindelsen 10 og katalysatoren er 1:0,05 til 0,6; molforholdet mellem forbindelsen 10 og saltsyre er 1:3 til 10; og forholdet mellem anvendelsesmængden af forbindelsen 10 og den af det alkoholholdige opløsningsmiddel eller ketonopløsningsmidlet er 1 g/5 til 25 ml.

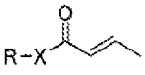
5. Syntetiseringsfremgangsmåde ifølge krav 4, **kendetegnet ved, at** i trin 1 er det polære opløsningsmiddel vand, methanol, ethanol eller isopropanol, fortrinsvis vand, methanol eller ethanol, optimalt vand; oxidationsmidlet er N-brombutanimid, meta-chloroperoxybenzoesyre, hydrogenperoxid med en koncentration på 35% eller en toluenopløsning af tert-butylhydroperoxid med en koncentration på 50%, fortrinsvis N-brombutanimid, meta-chloroperoxybenzoesyre eller en toluenopløsning af tert-butylhydroperoxid med en koncentration på 50% og optimalt N-brombutanimid; den stærke base er natriumhydroxid eller kaliumhydroxid, fortrinsvis natriumhydroxid; forholdet mellem anvendelsesmængden af forbindelsen med formlen



og den af det polære opløsningsmiddel er 1 g/5 til 15 ml, fortrinsvis 1 g/6 til 12 ml; molforholdet mellem forbindelsen med formlen



og oxidationsmidlet er 1:1 til 2,5, fortrinsvis 1:1 til 2; molforholdet mellem forbindelsen med formlen



og den stærke base er 1:1 til 2,5, fortrinsvis 1:1 til 2; i trin 2 er Lewis-syren fortrinsvis aluminiumchlorid, jernchlorid, zinkchlorid, en bortrifluorid-diethyletherat-opløsning med en koncentration på 47%, zinkbromid eller lithiumchlorid, fortrinsvis

aluminiumchlorid, bortrifluorid-diethyletheratopløsningen med en koncentration på 47%, zinkbromid eller lithiumchlorid og optimalt aluminiumchloriden; den uorganiske base er natriumbicarbonat, natriumcarbonat, natriumhydroxid, kaliumhydroxid, kaliumcarbonat eller kaliumbicarbonat, fortrinsvis natriumbicarbonat, natriumcarbonat, kaliumcarbonat eller kaliumbicarbonat, optimalt natriumcarbonat;

forholdet mellem anvendelsesmængden af forbindelsen 2 og den af acetone er 1:5 til 15, fortrinsvis 1:5 til 10; molforholdet mellem forbindelsen 2 og Lewis-syren er 1:0,1 til 0,8, fortrinsvis 1:0,1 til 0,6; forholdet mellem anvendelsesmængden af forbindelsen 2 og den af den uorganiske base er 1:0,5 til 2,5, fortrinsvis 1:0,5 til 1,5;

i trin 3 er det polære opløsningsmiddel fortrinsvis tetrahydrofuran, methanol eller ethanol, fortrinsvis tetrahydrofuran eller methanol, optimalt methanol; opløsningsreagensen er L-α-phenylethylamin eller L-α-amphetamin, fortrinsvis L-α-phenylethylamin; den alkaliske opløsning er en methanolopløsning af natriummethoxid med en koncentration på 29%, en vandig kaliumhydroxidopløsning med en koncentration på 20% eller en vandig natriumhydroxidopløsning med en koncentration på 20%, fortrinsvis methanolopløsningen af natriummethoxid med en koncentration på 29% eller den vandige kaliumhydroxidopløsning med en koncentration på 20%, optimalt methanolopløsningen af natriummethoxid med en koncentration på 29%; forholdet mellem anvendelsesmængden af forbindelsen 3 og den af det polære opløsningsmiddel er 1 g/3 til 8 ml, fortrinsvis 1 g/4 til 8 ml; molforholdet mellem forbindelsen 3 og rent vand er 1:0,5 til 1,8, fortrinsvis 1:0,5 til 1,5; molforholdet mellem forbindelsen 3 og den alkaliske substans i den alkaliske opløsning er 1:0,5 til 1,8, fortrinsvis 1:0,5 til 1,5; forholdet mellem anvendelsesmængden af forbindelsen 3 og den af det polære opløsningsmiddel til opløsning af filterkagen er 1 g/3 til 8 ml, fortrinsvis 1 g/3 til 7 ml; molforholdet mellem forbindelsen 3 og opløsningsreagensen er 1:1 til 4, fortrinsvis 1:1 til 3;

i trin 4 er etheropløsningsmidlet fortrinsvis tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether, 1,4-dioxan eller ether, fortrinsvis tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether eller 1,4-dioxan,

optimalt 2-methyltetrahydrofuran eller 1,4-dioxan; den uorganiske syre er svovlsyre, saltsyre eller fosforsyre, fortrinsvis svovlsyre eller saltsyre, optimalt svovlsyre; forholdet mellem anvendelsesmængden af forbindelsen 4 og den af etheropløsningsmidlet er 1 g/3 til 8 ml, fortrinsvis 1 g/3 til 6 ml; og molforholdet mellem forbindelsen 4 og N,N-diisopropylethylamin er 1:0,8 til 2,5, fortrinsvis 1:0,8 til 2;

i trin 5 er etheropløsningsmidlet fortrinsvis tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether, 1,4-dioxan eller ether, fortrinsvis tetrahydrofuran, 2-methyltetrahydrofuran eller methyl-tert-butylether, optimalt tetrahydrofuran eller 2-methyltetrahydrofuran; chloroformiatet er methylchloroformiat, ethylchloroformiat eller propylchloroformiat, fortrinsvis methylchloroformiat eller ethylchloroformiat, optimalt ethylchloroformiat; den alkaliske reagens er triethylamin, natriumcarbonat, kaliumcarbonat, natriumbicarbonat, kaliumbicarbonat, natriumhydroxid eller kaliumhydroxid, fortrinsvis triethylamin, natriumcarbonat, kaliumcarbonat, natriumhydroxid eller kaliumhydroxid, optimalt triethylamin; forholdet mellem anvendelsesmængden af forbindelsen 5 og den af etheropløsningsmidlet er 1 g/6 til 12 ml, fortrinsvis 1 g/8 til 12 ml; molforholdet mellem forbindelsen 5 og N,N-diisopropylethylamin er 1:1,5 til 4, fortrinsvis 1:2 til 4; molforholdet mellem forbindelsen 5 og chloroformiatet er 1:1 til 2,5, fortrinsvis 1:1 til 2; og molforholdet mellem forbindelsen 5 og hydrogenchlorid er 1:1,5 til 4,5, fortrinsvis 1:2 til 4;

i trin 6 er det polære opløsningsmiddel fortrinsvis acetonitril, methanol, ethanol, acetone eller tetrahydrofuran, fortrinsvis methanol, ethanol eller acetone, optimalt acetone; katalysatoren er natriumiodid eller kaliumiodid, fortrinsvis kaliumiodid; trinitiden er natriumazid eller azidotrimethylsilan, fortrinsvis natriumazid; forholdet mellem anvendelsesmængden af forbindelsen 6 og den af det polære opløsningsmiddel er 1 g/6 til 12 ml, fortrinsvis 1 g/8 til 12 ml; molforholdet mellem forbindelsen 6 og trinitriden er 1:1 til 3, fortrinsvis 1:1 til 2,5; og molforholdet mellem forbindelsen 6 og katalysatoren er 1:0,05 til 0,6, fortrinsvis 0,1 til 0,5.

6. Syntetiseringsfremgangsmåde ifølge krav 4, **kendetegnet ved, at** i trin 7 er etheropløsningsmidlet tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butyl-ether, 1,4-dioxan eller ether, fortrinsvis tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether eller 1,4-dioxan, optimalt tetrahydrofuran; syrereagensen er citronsyre, p-toluensulfonsyre, benzensulfonsyre, myresyre, eddikesyre, saltsyre, svovlsyre eller fosforsyre, fortrinsvis citronsyre, p-toluensulfonsyre, benzen-sulfonsyre, saltsyre eller svovlsyre, optimalt citronsyre eller saltsyre; forholdet mellem anvendelsesmængden af forbindelsen 7 og den af etheropløsningsmidlet er 1 g/5 til 12 ml, fortrinsvis 1 g/6 til 12 ml; molforholdet mellem forbindelsen 7 og triphenylphosphin er 1:0,6 til 2, fortrinsvis 1:0,8 til 2; forholdet mellem anvendel-sesmængden af forbindelsen 7 og den af vand er 1:0,6 til 2, fortrinsvis 1:0,8 til 2; masseforholdet mellem forbindelsen 7 og 5% palladium på carbon eller 10% palladium på carbon eller Raney-nikkel er 1:0,05 til 0,4, fortrinsvis 1:0,05 til 0,3; hydrogen indføres, indtil trykket i systemet er 0,5 til 0,8MPa, fortrinsvis 0,6 til 0,8MPa.

7. Syntetiseringsfremgangsmåde ifølge krav 4, **kendetegnet ved, at** i trin 8 er det alkoholholdige opløsningsmiddel methanol, ethanol, propanol eller iso-propanol, fortrinsvis methanol, ethanol eller isopropanol, optimalt isopropanol eller ethanol; katalysatoren er natriumiodid eller kaliumiodid, fortrinsvis natriumiodid; den alkaliske reagens er triethylamin, diisopropylethylamin, diisopropylamin, pyridin, natriumbicarbonat, kaliumbicarbonat, natriumcarbonat, kaliumcarbonat eller cæsiumcarbonat, fortrinsvis triethylamin, pyridin, natriumbicarbonat, kalium-bicarbonat, natriumcarbonat eller kaliumcarbonat, optimalt triethylamin; bufferopløsningen er en vandig natriumdihydrogenfosfat-dinatriumhydrogen-fosfatopløsning, en vandig kaliumdihydrogenfosfat-dikaliumhydrogenfosfatopløs-ning eller en vandig ammoniumformiat-ammoniakopløsning, fortrinsvis den vandige natriumdihydrogenfosfat-dinatriumhydrogenfosfatopløsning eller den vandige kaliumdihydrogenfosfat-dikaliumhydrogenfosfatopløsning, optimalt den vandige kaliumdihydrogenfosfat-dikaliumhydrogenfosfatopløsning; forholdet mel-lem anvendelsesmængden af forbindelsen 8 og den af det alkoholholdige

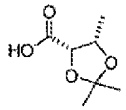
opløsningsmiddel er 1 g/6 til 12 ml, fortrinsvis 1 g/6 til 10 ml; forholdet mellem anvendelsesmængden af forbindelsen 8 og den af rent vand er 1 g/1 til 4 ml, fortrinsvis 1 g/1 til 3 ml; molforholdet mellem forbindelsen 8 og forbindelsen A er 1:1 til 1,4, fortrinsvis 1:1 til 1,2; molforholdet mellem forbindelsen 8 og katalysatoren er 1:0,1 til 0,4, fortrinsvis 1:0,1 til 0,3; og molforholdet mellem forbindelsen 8 og den alkaliske reagens er 1:4 til 7, fortrinsvis 1:4 til 6;

i trin 9 er katalysatoren fortrinsvis Raney-nikkel, 5% palladium på carbon, 10% palladium på carbon, platindioxid eller 20% palladium på carbon, fortrinsvis Raney-nikkel, 5% palladium på carbon eller 10% palladium på carbon, optimalt Raney-nikkel; det polære opløsningsmiddel er rent vand, methanol eller ethanol, fortrinsvis rent vand og methanol, optimalt rent vand; den alkaliske opløsning er natriumhydroxid, kaliumhydroxid, natriumcarbonat eller kaliumcarbonat, fortrinsvis natriumhydroxid eller natriumcarbonat, optimalt natriumhydroxid; forholdet mellem anvendelsesmængden af forbindelsen 9 og den af det polære opløsningsmiddel er 1 g/25 til 45 ml, fortrinsvis 1 g/30 til 40 ml, og masseforholdet mellem forbindelsen 9 og katalysatoren er 1:0,05 til 0,5, fortrinsvis 1:0,1 til 0,4;

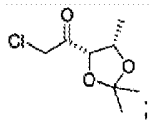
i trin 10 er katalysatoren fortrinsvis Raney-nikkel, 5% palladium på carbon, 10% palladium på carbon, platindioxid eller 20% palladium på carbon, fortrinsvis Raney-nikkel, platindioxid eller 20% palladium på carbon, optimalt 20% palladium på carbon; det alkoholholdige opløsningsmiddel er methanol, ethanol, isopropanol eller n-butanol, fortrinsvis methanol, ethanol eller isopropanol, optimalt methanol; ketonopløsningsmidlet er acetone eller butanon, fortrinsvis acetone; masseforholdet mellem forbindelsen 10 og katalysatoren er 1:0,05 til 0,5, fortrinsvis 1:0,1 til 0,4; molforholdet mellem forbindelsen 10 og saltsyre er 1:4 til 9, fortrinsvis 1:5 til 8; og forholdet mellem anvendelsesmængden af forbindelsen 10 og den af det alkoholholdige opløsningsmiddel eller ketonopløsningsmidlet er 1 g/5 til 20 ml, fortrinsvis 1 g/10 til 20 ml.

8. Fremgangsmåde til fremstilling af (3S,4S)-1-amino-3,4-dihydroxy-2-pentanon, **kendetegnet ved, at** den omfatter følgende trin:

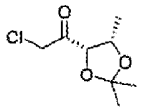
trin 1: at anvende en forbindelse 5 med formlen



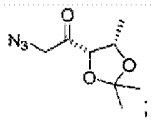
som et råmateriale til at syntetisere en forbindelse 6 med formlen



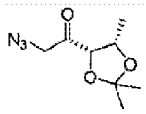
trin 2: at reagere forbindelsen 6 med formlen



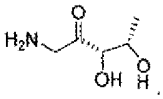
med en trinitrid for at frembringe en forbindelse 7 med formlen



trin 3: at underkaste forbindelsen 7 med formlen



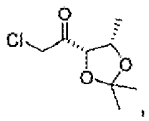
hydrogenering for at opnå en forbindelse 8 med formlen



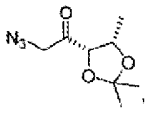
9. Fremgangsmåde ifølge krav 8, **kendetegnet ved**, **at** den omfatter følgende trin:

trin 1: at tilsætte forbindelsen 5 og N,N-diisopropylethylamin i nærvær af et etheropløsningsmiddel, at sænke temperaturen til -30°C til 0°C, at tilsætte et chloroformiat, at reagere i 1 til 2 timer, mens temperaturen opretholdes, at indføre en diazomethangas i 1 til 2 timer, at tilsætte en hydrochlorid-ethanolopløsning, at reagere i 1 til 2 timer, at tilsætte en alkalisk reagens

for at regulere pH-værdien til 7 til 9, at gennemføre ekstraktion, væskeseparation og koncentration for at opnå forbindelsen 6 med formlen

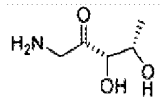


trin 2: at tilsætte forbindelsen 6, en trinitrid og en katalysator i nærvær af et polært opløsningsmiddel, at reagere systemet ved 15°C til 40°C i 20 til 30 timer, mens temperaturen opretholdes, derefter at gennemføre filtrering og koncentration for at opnå en opløsning forbindelsen 7 med formlen



der anvendes direkte i det næste trin;

trin 3: at tilsætte triphenylphosphin og vand eller palladium på carbon og hydrogen eller Raney-nikkel og hydrogen i nærvær af et etheropløsningsmiddel, at regulere systemets pH til 1 til 4 med en syrereagens, at tilsætte en opløsning af forbindelsen 7, at opretholde temperaturen ved 10°C til 30°C, at reagere i 5 til 10 timer, at gennemføre vakuumfiltrering og koncentration for at opnå et filtrat, der indeholder forbindelsen 8 med formlen



som anvendes direkte i det næste trin, eller et faststof separeres til anvendelse i det næste trin.

10. Fremgangsmåde ifølge krav 9, **kendetegnet ved, at** i trin 1 er forholdet mellem anvendelsesmængden af forbindelsen 5 og den af etheropløsningsmidlet 1 g/5 til 15 ml; molforholdet mellem forbindelsen 5 og N,N-diisopropylethylamin er 1:1 til 5; molforholdet mellem forbindelsen 5 og chloroformiatet er 1:1 til 3; og molforholdet mellem forbindelsen 5 og hydrogenchlorid er 1:1 til 5.

11. Fremgangsmåde ifølge krav 10, **kendetegnet ved, at** i trin 1 er etheropløsningsmidlet tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether, 1,4-

dioxan eller ether; chloroformiatet er methylchloroformiat, ethylchloroformiat eller propylchloroformiat; den alkaliske reagens er triethylamin, natriumcarbonat, kaliumcarbonat, natriumbicarbonat, kaliumbicarbonat, natriumhydroxid eller kaliumhydroxid; forholdet mellem anvendelsesmængden af forbindelsen 5 og den af etheropløsningsmidlet er 1 g/6 til 12 ml, fortrinsvis 1 g/8 til 12 ml; molforholdet mellem forbindelsen 5 og N,N-diisopropylethylamin er 1:1,5 til 4, fortrinsvis 1:2 til 4; molforholdet mellem forbindelsen 5 og chloroformiatet er 1:1 til 2,5, fortrinsvis 1:1 til 2; og molforholdet mellem forbindelsen 5 og hydrogenchlorid er 1:1,5 til 4,5, fortrinsvis 1:2 til 4.

12. Fremgangsmåde ifølge krav 9, **kendetegnet ved, at** i trin 2 er forholdet mellem anvendelsesmængden af forbindelsen 6 og den af det polære opløsningsmiddel 1 g/5 til 15 ml; molforholdet mellem forbindelsen 6 og trinitriden er 1:1 til 4; og molforholdet mellem forbindelsen 6 og katalysatoren er 1:0,05 til 0,8.

13. Fremgangsmåde ifølge krav 12, **kendetegnet ved, at** det polære opløsningsmiddel er acetonitril, methanol, ethanol, acetone eller tetrahydrofuran; katalysatoren er natriumiodid eller kaliumiodid; trinitriden er natriumazid eller azidotrimethylsilan; forholdet mellem anvendelsesmængden af forbindelsen 6 og den af de polære opløsningsmiddel er 1 g/6 til 12 ml, fortrinsvis 1 g/8 til 12 ml; molforholdet mellem forbindelsen 6 og trinitriden er 1:1 til 3, fortrinsvis 1:1 til 2,5; og molforholdet mellem forbindelsen 6 og katalysatoren er 1:0,05 til 0,6, fortrinsvis 0,1 til 0,5.

14. Fremgangsmåde ifølge krav 9, **kendetegnet ved, at** i trin 3 er forholdet mellem anvendelsesmængden af forbindelsen 7 og den af etheropløsningsmidlet 1 g/5 til 15 ml; molforholdet mellem forbindelsen 7 og triphenylphosphin er 1:0,1 til 3; forholdet mellem anvendelsesmængden af forbindelsen 7 og den af vand er 1:0,1 til 3; masseforholdet mellem forbindelsen 7 og 5% palladium på carbon eller 10% palladium på carbon eller Raney-nikkel er 1:0,05 til 0,6; at indføre hydrogen, indtil trykket i systemet er 0,4 til 0,9MPa.

15. Fremgangsmåde ifølge krav 14, **kendetegnet ved, at** etheropløsningsmidlet er tetrahydrofuran, 2-methyltetrahydrofuran, methyl-tert-butylether, 1,4-dioxan eller ether; syrereagensen er citronsyre, p-toluensulfonsyre, benzensulfonsyre, myresyre, eddikesyre, saltsyre, svovlsyre eller fosforsyre; forholdet mellem anvendelsesmængden af forbindelsen 7 og den af etheropløsningsmidlet er 1 g/5 til 12 ml, fortrinsvis 1 g/6 til 12 ml; molforholdet mellem forbindelsen 7 og triphenylphosphin is 1:0,6 til 2, fortrinsvis 1:0,8 til 2; forholdet mellem anvendelsesmængden af forbindelsen 7 og den af vand er 1:0,6 til 2, fortrinsvis 1:0,8 til 2; masseforholdet mellem forbindelsen 7 og 5% palladium på carbon eller 10% palladium på carbon eller Raney-nikkel er 1:0,05 til 0,4, fortrinsvis 1:0,05 til 0,3; at indføre hydrogen, indtil trykket i systemet er 0,5 til 0,8MPa, fortrinsvis 0,6 til 0,8MPa.

DRAWINGS

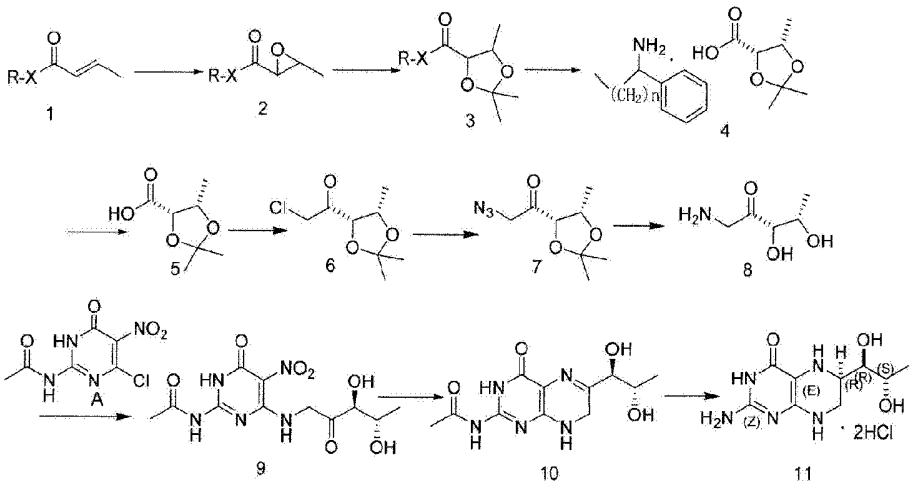


Fig. 1