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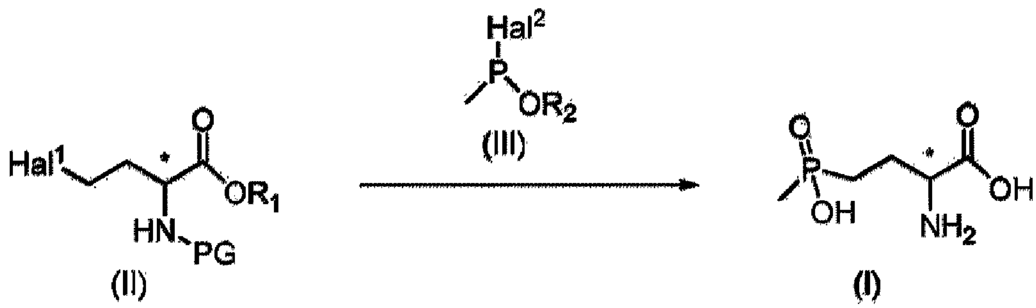
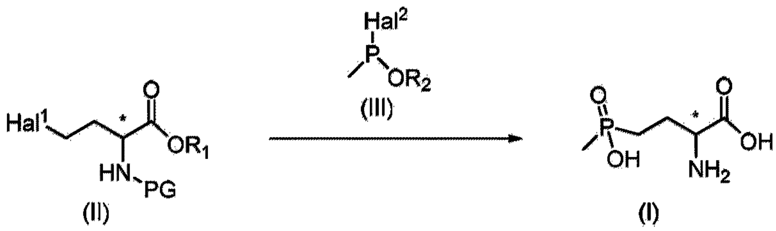
(54) Titre : METHODE DE PREPARATION DE GLUFOSINATE
(54) Title: PREPARATION METHOD FOR GLUFOSINATE



(57) Abrégé/Abstract:
Provided herein is a preparation method for glufosinate of formula (I) or a salt thereof, an enantiomer thereof, or mixtures of the enantiomer thereof in all ratios, comprising reacting a compound of formula (II) or a salt, an enantiomer, or mixtures of the enantiomer in all ratios with one or more compounds of formula (III) or mixtures thereof. The preparation method is highly efficient, and avoids use of toxic reagents which are necessary in existing methods.

Abstract



Provided herein is a preparation method for glufosinate of formula (I) or a salt thereof, an enantiomer thereof, or mixtures of the enantiomer thereof in all ratios, comprising reacting a compound of formula (II) or a salt, an enantiomer, or mixtures of the enantiomer in all ratios with one or more compounds of formula (III) or mixtures thereof. The preparation method is highly efficient, and avoids use of toxic reagents which are necessary in existing methods.

Preparation method for glufosinate

Technical Field

The present invention relates to a preparation method for glufosinate.

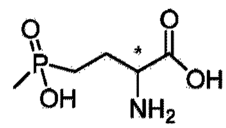
Background Art

Glufosinate is an important herbicide. It is a highly potent, broad-spectrum, low toxicity, non-selective (sterilant) organophosphorus herbicide with certain systemic action developed by Hoechst in the 1980s. It can control annual or perennial dicotyledon weeds and gramineae weeds.

Existing methods for preparing glufosinate have complex processes and high costs. For example, the method most commonly used for preparing glyphosate in the industrial production is the Strecker method (see e.g., US6359162B1). In this method, after the addition reaction between methyl phosphite and acrolein, a Strecker reaction is performed, and the final product is then obtained by hydrolysis and purification. However, this preparation method comprises multiple steps, and employs highly toxic reagents such as sodium cyanide.

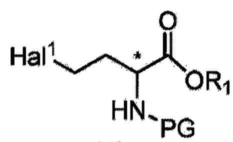
Contents of the Invention

The present invention provides a method for preparing glufosinate of formula (I) or a salt, an enantiomer thereof or a mixture of the enantiomers in all ratios, comprising the following steps:



(I)

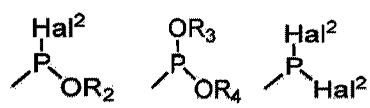
a) reacting a compound of formula (II) or a salt, an enantiomer thereof or a mixture of the enantiomers in all ratios,



(II)

with one or more compounds of formula (III) or a mixture;

the above mixture being a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V); or a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V);



(III) (IV) (V)

b) reacting the intermediate, no matter whether it is isolated or not, in the presence of water and an acid or a base to obtain the glufosinate (I) or a salt, an enantiomer thereof or a mixture of

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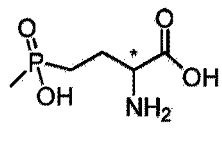
the enantiomers in all ratios;

wherein when PG is an amino protecting group, a step of removing the amino protecting group can be further comprised;

wherein Hal^1 and Hal^2 are each independently halogen; PG is hydrogen or an amino protecting group; R_1, R_2, R_3 and R_4 are each independently alkyl, phenyl or substituted phenyl, and when the mixture comprises the mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), or when the mixture comprises the mixture of one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V), R_2 is either R_3 or R_4; and the chiral carbon atom is labeled with *.

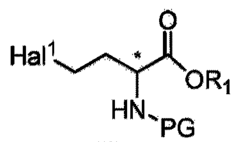
The present invention further provides a method for preparing enantiomerically pure glufosinate of formula (I) or a salt thereof,



(I)

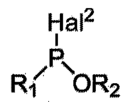
the method comprises the following steps:

a1) reacting an enantiomerically pure compound of formula (II) or a salt thereof,



(II)

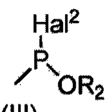
with a compound of formula (III),



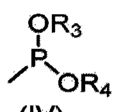
(III)

or one or more compounds of formula (III) or a mixture;

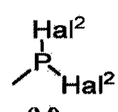
the above mixture being a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V); or a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V);



(III)



(IV)



(V)

b1) reacting the intermediate, no matter whether it is isolated or not, in the presence of water and an acid or a base to obtain the enantiomerically pure glufosinate (I) or a salt thereof;

wherein when PG is an amino protecting group, a step of removing the amino protecting group can be further comprised;

wherein Hal^1 and Hal^2 are each independently halogen; PG is hydrogen or an amino protecting group; R_1, R_2, R_3 and R_4 are each independently alkyl, phenyl or substituted phenyl,

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and when the mixture comprises the mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), or when the mixture comprises the mixture of one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V), R_2 is either R_3 or R_4; and the chiral carbon atom is labeled with *.

In certain specific embodiments, one compound of formula (III), e.g., chloro(ethoxy)(methyl)phosphane, is employed.

In certain specific embodiments, a mixture of one compound of formula (IV) and one compound of formula (V) is employed, such as a mixture of dichloro(methyl)phosphane and diethyl methylphosphonite, and the mixture can be further added with a compound of formula (III), e.g., chloro(ethoxy)(methyl)phosphane, in any ratio.

Further, the enantiomeric ratio is (L):(D)-enantiomer or (D):(L)-enantiomer of 50.5:49.5 to 99.5:0.5.

Further, the enantiomeric ratio is (L):(D)-enantiomer of 50.5:49.5 to 99.5:0.5.

Further, the PG is hydrogen.

Further, the Hal^1 is a chlorine atom.

Further, the Hal^2 is a chlorine atom.

Further, the R_1, R_2, R_3 and R_4 are each independently C_1-C_6 alkyl, preferably C_1-C_4 alkyl.

Further, the R_1 is ethyl.

Further, the R_2 is ethyl.

Further, the R_3 is ethyl.

Further, the R_4 is ethyl.

In certain specific embodiments, the mixture is a mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.9-1.1):1 or (0.05-1.1):1; or the mixture is a mixture of one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.9-1.1):1 or (0.05-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V), and the molar ratio of the compounds of formula (IV) to the compounds of formula (V) is (0.9-1.1):1.

Further, in aforementioned step a) or a1), the reaction can proceed at room temperature, the reaction temperature can be 20-200 °C, and preferably 90-140 °C in consideration of reaction efficiency.

Further, the aforementioned step a) or a1) is carried out in the presence of a base.

Further, the base in aforementioned step a) or a1) is an organic base or ammonia.

Further, in aforementioned step a) or a1), the organic base is selected from the group consisting of an organic amine, pyridine or a pyridine derivative having 1-3 substituents attached to one or more carbon atoms in the heterocycle, piperidine or a piperidine derivative having 1-3 substituents attached to one or more carbon atoms in the heterocycle.

Further, the organic base is selected from the group consisting of triethylamine, piperidine or pyridine.

Further, in aforementioned step a) or a1), the molar ratio of the base to the total amounts of the compound of formula (III) and the compound of formula (V) is (1-10):1.

Further, in aforementioned step a) or a1), the reaction is carried out under a solvent-free condition or in an inert solvent.

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Further, in aforementioned step a) or a1), the inert solvent is selected from any one or more of benzene solvents, amide solvents, hydrocarbon solvents, halogenated hydrocarbon solvents, sulfone or sulfoxide solvents, ether solvents or ester solvents; preferably, the inert solvent is selected from any one or more of benzene solvents, amide solvents, halogenated hydrocarbon solvents, ether solvents or ester solvents.

Further, in aforementioned step a) or a1), the inert solvent is selected from any one or more of chlorobenzene, trimethylbenzene, 1,4-dioxane, 1,2-dichloroethane, dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylformamide, petroleum ether, n-heptane, tetrahydrofuran, methyltetrahydrofuran, benzene, toluene, ethyl acetate, and butyl acetate.

Further, in aforementioned step a) or a1), the molar ratio of the compound of formula (III) or the mixture to the compound of formula (II) is 1:(0.8-10), preferably 1:(1-3); or the molar ratio of the compound of formula (II) to the compound of formula (III) or the mixture is 1:(0.8-10), preferably 1:(1-3).

Further, in aforementioned step b) or b1), an inorganic acid or an organic acid is added.

Further, the inorganic acid is hydrochloric acid or sulfuric acid.

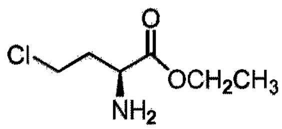
Further, in aforementioned step b) or b1), the base is an inorganic base or an organic base.

Further, the base is alkali metal hydroxide, alkali-earth metal hydroxide, alkali metal carbonate, alkali-earth metal carbonate, alkali metal bicarbonate or alkali-earth metal bicarbonate.

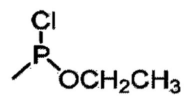
Further, the base is NaOH, KOH or $Ba(OH)_2$.

Further, in aforementioned step b) or b1), the reaction temperature is 20-150 °C.

As a specific embodiment, a compound of formula (IIa) is reacted with a compound of formula (IIIa),



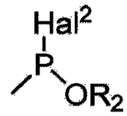
(IIa)



(IIIa)

and an acid (e.g., hydrochloric acid) is then added to obtain L-glufosinate.

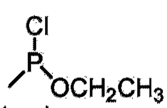
The present invention further provides a compound of formula (III)



(III)

wherein Hal^2 and R_2 are as defined above.

The present invention further provides use of the compound of formula (III), particularly a compound of formula (IIIa), in the preparation of glufosinate or a salt thereof, or L-glufosinate or a salt thereof,



(IIIa)

The present invention further provides a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V); or a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising

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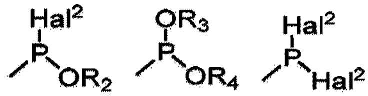
one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V);



(III) (IV) (V)

wherein Hal^2, R_2, R_3 and R_4 are as defined above.

Further, the above mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V), and the molar ratio of the compounds of formula (IV) to the compounds of formula (V) is (0.9-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.9-1.1):1 or (0.05-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.9-1.1):1 or (0.05-1.1):1.

Further, the compound of formula (IV) is diethyl methylphosphonite, and the compound of formula (V) is dichloro(methyl)phosphane.

The present invention further provides use of the aforementioned mixture in the preparation of glufosinate or a salt thereof, or L-glufosinate or a salt thereof.

The method of the present invention is particularly suitable for the preparation of glufosinate, and substantially reduces the steps of the existing preparation processes. In particular, in the preparation of L-glufosinate, the product can effectively maintain the ee value of the raw material. For example, when an enantiomerically pure raw material (e.g., the enantiomeric excess percentage (% ee) is greater than 90%) is employed, the enantiomeric excess percentage (% ee) of the prepared L-glufosinate is greater than e.g., 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%.

Unless otherwise specified, the terms used in the specification and claims have the following meanings.

The term "amino protecting group" refers to a group that can be attached to a nitrogen atom in an amino group to protect the amino group from participating the reaction and can be easily removed in the subsequent reactions. Suitable amino protecting groups include, but are not limited to, the following protecting groups:

carbamate group of formula -C(O)O-R, wherein R is methyl, ethyl, *tert*-butyl, benzyl, phenethyl, CH_2=CH-CH_2-, *etc.*; amide group of formula -C(O)-R', wherein R' is methyl, ethyl, phenyl, trifluoromethyl, *etc.*; N-sulfonyl derivative group of formula -SO_2-R", wherein R" is tolyl, phenyl, trifluoromethyl, 2,2,5,7,8-pentamethylchroman-6-yl-, 2,3,6-trimethyl-4-methoxybenzene, *etc.*

The term "alkyl" refers to a saturated aliphatic hydrocarbon group, including linear and branched groups having 1 to 18 carbon atoms. Alkyl having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, 2-propyl, n-butyl, isobutyl, *tert*-butyl and pentyl, is preferred. The alkyl can be substituted or unsubstituted, and when substituted, the substituent can be halogen, nitro, sulfonyl, ether oxy, ether thio, ester, thioester or cyano.

The C_1-C_4 alkyl is linear or branched, comprising saturated hydrocarbon chain having 1 to 4 carbon atoms. It can be methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or *tert*-butyl.

The "mixture of the enantiomers in all ratios" as used herein has the same meaning as the "mixture of the enantiomers in any ratio".

Mode of Carrying Out the Invention

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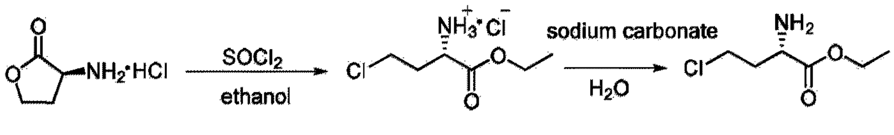
Preparation of compound 1



10 g of L-homoserine lactone hydrochloride (ee value of 99%, 137.56 g/mol, 0.073 mol) was weighed into a reaction flask, and 50 mL of ethanol (46.07 g/mol, 0.886 mol, 0.816 g/mL) was added (the molar ratio of homoserine lactone hydrochloride to ethanol is 1:12.1). The system was cooled to 10 °C, and 21.7 g of thionyl chloride (118.97 g/mol, 0.182 mol) was slowly dropwise added (the molar ratio of L-homoserine lactone hydrochloride to thionyl chloride is 1:2.5). The system temperature was maintained at 10 °C, and stirred for 30 minutes. The reaction was heated to 35 °C, and stirred for 20 h, during which bubbles were continuously generated. The reaction was monitored by LC-MS. The reaction was stopped, the system was cooled to room temperature, and the remaining thionyl chloride and ethanol were distilled off under reduced pressure. The solid residue was slurried with 30 mL of n-hexane/ethyl acetate mixed solvents (the volume ratio of n-hexane to ethyl acetate is 2:1), filtered and dried to obtain 13.69 g of chloro-homoserine ethyl ester hydrochloride (202.08 g/mol, 0.0657 mol), wherein the HPLC purity is 97%, and the yield calculated on the basis of the amount of the reactant L-homoserine lactone hydrochloride is 90%.

The chloro-homoserine ethyl ester hydrochloride solid was reacted with a saturated sodium carbonate solution. The system was adjusted to a pH of 7-8, and extracted with ethyl acetate for 3 times, wherein the amounts of ethyl acetate in the 3 extraction processes were 30 mL, 10 mL and 10 mL, respectively. The organic phases were collected, and concentrated to obtain 10.30 g of the oily target product, chloro-homoserine ethyl ester (165.62 g/mol, 0.0591 mol), wherein the HPLC purity was 95%, the ee value was 99%, and the yield calculated based on the intermediate product chloro-homoserine ethyl ester hydrochloride was 90%.

MS (ESI): m/z $[M + H]^+$ calculated for C6H13ClNO2: 166.06, found: 166.0.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.04 (q, J =7.1 Hz, 2H), 3.65 – 3.50 (m, 2H), 3.48 (dd, J =9.0, 4.7 Hz, 1H), 2.05 (dddd, J =14.7, 8.5, 6.4, 4.6 Hz, 1H), 1.87 – 1.64 (m, 3H), 1.13 (t, J =7.2 Hz, 3H).

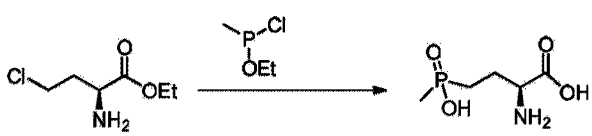
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.3, 61.0, 51.6, 41.5, 37.0, 14.1.

Example 1

Under a nitrogen atmosphere, diethyl methylphosphonite (65.9 g, 484.8 mmol,1.0 eq) and a solvent 1,4-dioxane (66 g) were added to a round-bottom flask, a 1,4-dioxane (63 g) solution of dichloro(methyl)phosphane (62.3 g, 533.3 mmol, 1.1 eq) were dropwise added through a constant-pressure funnel, and the reaction was stirred at room temperature overnight. 1,4-dioxane and chloro(ethoxy)(methyl)phosphane (colorless liquid, 85.8 g, yield: 70%) were distilled out under reduced pressure.

^{1}H NMR (D_2O, 43 MHz) δ: 3.92 – 2.96 (m, 2H), 1.31 (d, J =12.8 Hz, 3H), 0.84 (t, J =7.0 Hz, 3H).

Example 2



1 2

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Under a nitrogen atmosphere, compound 1 (40.0 g, 242.4 mmol, 1.0 eq), chlorobenzene (81.9 g, 727.2 mmol, 3.0 eq) and triethylamine (29.4 g, 290.9 mmol, 1.2 eq) were respectively added to a three-neck flask, chloro(ethoxy)(methyl)phosphane (36.8 g, 290.9 mmol, 1.2 eq) was dropwise added, and the reaction was stirred at room temperature for 2 hours. The reaction was heated to 100 °C, and allowed to proceed for 20 h. MS detection indicated that the raw material disappeared. The reaction was cooled to room temperature, dropwise added with 36% HCl (294.9 mL, 3432.6 mmol, 14.0 eq), and heated to reflux until complete reaction of the starting material. The solvent was evaporated, 95% ethanol (200 mL) and water (20 mL) were added, and the mixture was heated to reflux until the product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain L-glufosinate (white crystal, 38.4 g, yield: 88%, 98% ee).

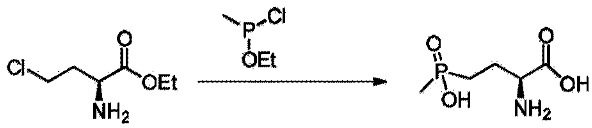
MS (ESI): m/z $[M + H]^+$ calculated for C5H13NO4P: 182.05, found 182.1.

^{1}H NMR (D_2O, 400 MHz) δ: 4.08 (t, J =6.2 Hz, 1H), 2.11 (dddd, J =14.6, 11.0, 8.7, 6.0 Hz, 2H), 1.99 – 1.73 (m, 2H), 1.44 (d, J =14.2 Hz, 3H).

^{13}C NMR (D_2O, 100 MHz) δ: 171.0, 52.8, 52.6, 25.5, 24.6, 22.6, 22.5, 13.9, 13.0.

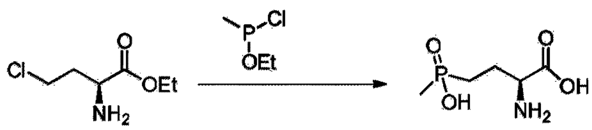
^{31}P NMR (D_2O, 160 MHz) δ: 53.8.

Example 3



Under a nitrogen atmosphere, compound 1 (40.0 g, 242.4 mmol, 1.0 eq), chlorobenzene (81.9 g, 727.2 mmol, 3.0 eq) and pyridine (23.0 g, 290.9 mmol, 1.2 eq) were respectively added to a three-neck flask, chloro(ethoxy)(methyl)phosphane (36.8 g, 290.9 mmol, 1.2 eq) was dropwise added, and the reaction was stirred at room temperature for 2 hours. The reaction was heated to 100 °C, and allowed to proceed for 20 h. MS detection indicated that the raw material disappeared. The reaction was cooled to room temperature, dropwise added with 36% HCl (294.9 mL, 3432.6 mmol, 14.0 eq), and heated to reflux until complete reaction of the starting material. The solvent was evaporated, 95% ethanol (200 mL) and water (20 mL) were added, and the mixture was heated to reflux until the product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain L-glufosinate (white crystal, 35.3 g, yield: 81%, 96% ee).

Example 4



Under a nitrogen atmosphere, compound 1 (40.0 g, 242.4 mmol, 1.0 eq), chlorobenzene (81.9 g, 727.2 mmol, 3.0 eq) and piperidine (24.8 g, 290.9 mmol, 1.2 eq) were respectively added to a three-neck flask, chloro(ethoxy)(methyl)phosphane (36.8 g, 290.9 mmol, 1.2 eq) was dropwise added, and the reaction was stirred at room temperature for 2 hours. The reaction was heated to 100 °C, and allowed to proceed for 20 h. MS detection indicated that the raw material disappeared. The reaction was cooled to room temperature, dropwise added with 36% HCl (294.9 mL, 3432.6 mmol, 14.0 eq), and heated to reflux until complete reaction of the starting material. The solvent was evaporated, 95% ethanol (200 mL) and water (20 mL) were added, and the mixture was heated to reflux until the product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain L-glufosinate (white crystal, 33.2 g, yield: 76%, 94% ee).

Example 5

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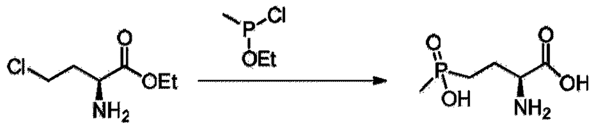
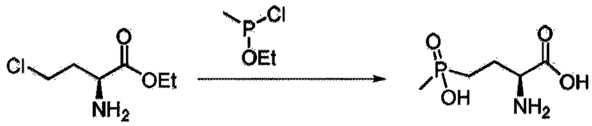


1 2

Under a nitrogen atmosphere, compound 1 (40.0 g, 242.4 mmol, 1.0 eq) and chlorobenzene (81.9 g, 727.2 mmol, 3.0 eq) were respectively added to a three-neck flask. Chloro(ethoxy)(methyl)phosphane (36.8 g, 290.9 mmol, 1.2 eq) was dropwise added, and ammonia was simultaneously bubbled in until saturation. The reaction was stirred at room temperature for 2 hours. The reaction was heated to 100 °C, and allowed to proceed for 20 h. MS detection indicated that the raw material disappeared. The reaction was cooled to room temperature, dropwise added with 36% HCl (294.9 mL, 3432.6 mmol, 14.0 eq), and heated to reflux until complete reaction of the starting material. The solvent was evaporated, 95% ethanol (200 mL) and water (20 mL) were added, and the mixture was heated to reflux until the product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain L-glufosinate (white crystal, 38 g, yield: 87%, 97% ee).

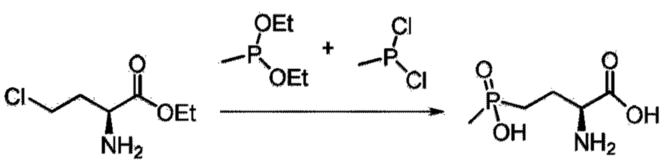
Example 6



1 2

Under a nitrogen atmosphere, compound 1 (40.0 g, 242.4 mmol, 1.0 eq), 1,4-dioxane (64 g, 727.2 mmol, 3.0 eq) and triethylamine (29.4 g, 290.9 mmol, 1.2 eq) were respectively added to a three-neck flask, chloro(ethoxy)(methyl)phosphane (36.8 g, 290.9 mmol, 1.2 eq) was dropwise added, and the reaction was stirred at room temperature for 2 hours. The reaction was heated to 100 °C, and allowed to proceed for 20 h. MS detection indicated that the raw material disappeared. The reaction was cooled to room temperature, dropwise added with 36% HCl (294.9 mL, 3432.6 mmol, 14.0 eq), and heated to reflux until complete reaction of the starting material. The solvent was evaporated, 95% ethanol (200 mL) and water (20 mL) were added, and the mixture was heated to reflux until the product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain L-glufosinate (white crystal, 36.2 g, yield: 83%, 97% ee).

Example 7



1 2

Under a nitrogen atmosphere, dichloro(methyl)phosphane (520.5 mmol, 0.6 eq, purity: 90%) was added to a round-bottom flask at room temperature (20 °C), diethyl methylphosphonite (1735 mmol, 2.0 eq, purity: 98%) was dropwise added through a constant-pressure funnel, and the reaction was continuously stirred for 10 minutes after the dropwise addition. A solution of compound 1 (867.5 mmol, 1.0 eq, purity: 96%, ee value: 99%) and triethylamine (107.5 g, 1041 mmol, 1.2 eq, purity: 98%) in 1,4-dioxane (500 g) was dropwise added, and the reaction was continuously stirred for 1.5 hours after the dropwise addition. The reaction solution was then heated to 90 °C, and allowed to proceed for 20 h. The reaction solution was cooled to room temperature, and filtered with suction, the filter cake was washed with 1,4-dioxane (150 mL * 3), and the filtrate was rotary evaporated to remove 1,4-dioxane. The reaction was added with 100 mL of concentrated hydrochloric acid (36%), heated to 90 °C, and allowed to proceed for 10 hours. The solvent was rotary evaporated to dryness, 200 mL of concentrated hydrochloric acid (36%) was supplemented, and the reaction was continued at 90 °C for 10 hours. MS detection indicated

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the intermediate disappeared, and analysis of the reaction solution at this time indicated that the enantiomeric excess percentage (% ee) of L-glufosinate in the reaction solution was 92%. The reaction solution was cooled to room temperature, rotary evaporated to remove the solvent, added with 95% ethanol (300 mL), and heated to reflux until the crude product was completely dissolved. The mixture was cooled and crystallized, filtered, and dried to obtain the compound of L-glufosinate (yield: 69%, 97% ee).

In addition to those described herein, according to the foregoing description, various modifications to the present invention would be apparent to those skilled in the art. Such modifications are intended to fall within the scope of the appended claims.

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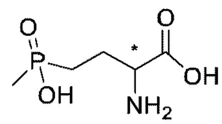
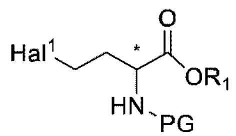
What is claimed is

1. A method for preparing glufosinate of formula (I) or a salt, an enantiomer thereof or a mixture of the enantiomers in all ratios, characterized in that the method comprises the following steps:



(I)

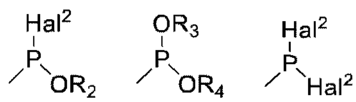
a) reacting a compound of formula (II) or a salt, an enantiomer thereof or a mixture of the enantiomers in all ratios,



(II)

with one or more compounds of formula (III) or a mixture to obtain an intermediate;

the mixture being a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V); or a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V);



(III) (IV) (V)

b) reacting the intermediate, no matter whether it is isolated or not, in the presence of water and an acid or a base to obtain the glufosinate of formula (I) or a salt, an enantiomer thereof or a mixture of the enantiomers in all ratios;

wherein

Hal^1 and Hal^2 are each independently halogen;

PG is hydrogen or an amino protecting group; when PG is an amino protecting group, the method further comprises a step of removing the amino protecting group;

R_1, R_2, R_3 and R_4 are each independently alkyl, phenyl or substituted phenyl, and when the mixture comprises the mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), or when the mixture comprises the mixture of one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V), R_2 is either R_3 or R_4; and

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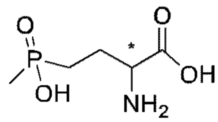
the chiral carbon atom is labeled with *.

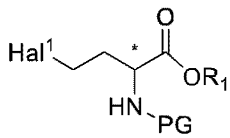
2. The method according to claim 1, wherein the method is for preparing enantiomerically pure glufosinate of formula (I) or a salt thereof,



(I)

characterized in that the method comprises the following steps:

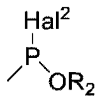
a1) reacting an enantiomerically pure compound of formula (II) or a salt thereof,



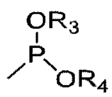
(II)

with one or more compounds of formula (III) or a mixture to obtain an intermediate,

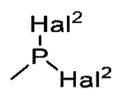
the mixture being a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V); or a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V);



(III)



(IV)



(V)

b1) reacting the intermediate, no matter whether it is isolated or not, in the presence of water and an acid or a base to obtain the enantiomerically pure glufosinate of formula (I) or a salt thereof;

wherein

Hal^1 and Hal^2 are each independently halogen;

PG is hydrogen or an amino protecting group; when PG is an amino protecting group, the method further comprises a step of removing the amino protecting group;

R_1, R_2, R_3 and R_4 are each independently alkyl, phenyl or substituted phenyl, and when the mixture comprises the mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), or when the mixture comprises the mixture of one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V), R_2 is either R_3 or R_4; and

the chiral carbon atom is labeled with *.

3. The method according to claim 1, characterized in that the enantiomeric ratio

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is (L):(D)-enantiomer or (D):(L)-enantiomer of 50.5:49.5 to 99.5:0.5.

4. The method according to claim 3, characterized in that the enantiomeric ratio is (L):(D)-enantiomer of 50.5:49.5 to 99.5:0.5.

5. The method according to any one of claims 1-4, characterized in that the PG is hydrogen.

6. The method according to any one of claims 1-5, characterized in that the Hal^1 is a chlorine atom.

7. The method according to any one of claims 1-6, characterized in that the Hal^2 is a chlorine atom.

8. The method according to any one of claims 1-7, characterized in that the R_1, R_2, R_3 and R_4 are each independently C_1-C_6 alkyl.

9. The method according to claim 8, characterized in that the R_1, R_2, R_3 and R_4 are each independently C_1-C_4 alkyl.

10. The method according to any one of claims 1-9, characterized in that the R_1 is ethyl.

11. The method according to any one of claims 1-10, characterized in that the R_2 is ethyl.

12. The method according to any one of claims 1-11, characterized in that the R_3 is ethyl.

13. The method according to any one of claims 1-12, characterized in that the R_4 is ethyl.

14. The method according to any one of claims 1-13, characterized in that the mixture is a mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.05-1.1):1; or the mixture is a mixture of one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.05-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V), and the molar ratio of the compounds of formula (IV) to the compounds of formula (V) is (0.9-1.1):1.

15. The method according to claim 14, characterized in that the mixture is a mixture of one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.9-1.1):1; or the mixture is a mixture of one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.9-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (V), and the molar ratio of the compounds of formula (IV) to the compounds of formula (V) is (0.9-1.1):1.

16. The method according to any one of claims 1-15, characterized in that the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture is carried out at a temperature of 20 to 200 °C.

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17. The method according to claim 16, characterized in that the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture is carried out at a temperature of 90 to 140 °C.

18. The method according to any one of claims 1-17, characterized in that the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture is carried out in the presence of a base.

19. The method according to claim 18, characterized in that the base in the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture is an organic base or ammonia.

20. The method according to claim 19, characterized in that the organic base is an organic amine.

21. The method according to claim 19, characterized in that the organic base is selected from the group consisting of pyridine, and piperidine.

22. The method according to claim 19, characterized in that the organic base is selected from the group consisting of triethylamine, piperidine and pyridine.

23. The method according to any one of claims 1-22, characterized in that in the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture, the molar ratio of the base to the total amounts of the compound of formula (III) and the compound of formula (V) is (1-10):1.

24. The method according to any one of claims 1-23, characterized in that the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture is carried out under a solvent-free condition or in an inert solvent.

25. The method according to claim 24, characterized in that the inert solvent is selected from any one or more of amide solvents, hydrocarbon solvents, halogenated hydrocarbon solvents, sulfone solvents, sulfoxide solvents, ether solvents and ester solvents.

26. The method according to claim 24, characterized in that the inert solvent is selected from any one or more of benzene solvents, amide solvents, halogenated hydrocarbon solvents, ether solvents and ester solvents.

27. The method according to claim 26, characterized in that the inert solvent is a benzene solvent.

28. The method according to claim 24, characterized in that the inert solvent is selected from any one or more of chlorobenzene, trimethylbenzene, 1,4-dioxane, 1,2-dichloroethane, dimethyl sulfoxide, N-methylpyrrolidone, N,N-dimethylformamide, petroleum ether, n-heptane, tetrahydrofuran, methyltetrahydrofuran, benzene, toluene, ethyl acetate, and butyl acetate.

29. The method according to any one of claims 1-28, characterized in that in the reaction of the compound of formula (II) with one or more compounds of formula (III) or the mixture, the molar ratio of the compound of formula (III) or the mixture to the compound of formula (II) is 1:(0.8-10); or the molar ratio of the compound of formula (II) to the compound of formula (III) or the mixture is 1:(0.8-10).

30. The method according to claim 29, characterized in that the molar ratio of the

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compound of formula (III) or the mixture to the compound of formula (II) is 1:(1-3); or the molar ratio of the compound of formula (II) to the compound of formula (III) or the mixture is 1:(1-3).

31. The method according to any one of claims 1-30, characterized in that in the reaction of the intermediate to obtain glufosinate of formula (I), an inorganic acid or an organic acid is added.

32. The method according to claim 31, characterized in that the inorganic acid is hydrochloric acid or sulfuric acid.

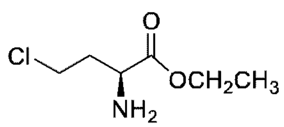
33. The method according to any one of claims 1-32, characterized in that in the reaction of the intermediate to obtain glufosinate of formula (I), the base is an inorganic base or an organic base.

34. The method according to claim 33, characterized in that the base is alkali metal hydroxide, alkali-earth metal hydroxide, alkali metal carbonate, alkali-earth metal carbonate, alkali metal bicarbonate or alkali-earth metal bicarbonate.

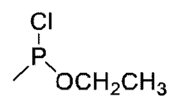
35. The method according to claim 33, characterized in that the base is NaOH, KOH or $Ba(OH)_2$.

36. The method according to any one of claims 1-35, characterized in that the reaction of the intermediate to obtain glufosinate of formula (I) is conducted at a temperature of 20 to 150 °C.

37. The method according to claim 1, wherein the method is for preparing L-glufosinate or a salt thereof, characterized in that a compound of formula (IIa) is reacted with a compound of formula (IIIa),



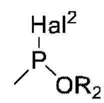
(IIa)



(IIIa)

and an acid is then added to obtain L-glufosinate.

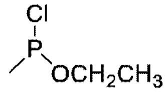
38. The method according to claim 37, wherein the acid is hydrochloric acid.



39. Use of a compound of formula (III): (III)

wherein Hal^2 and R_2 are as defined in any one of claims 1-13 in the preparation of glufosinate or a salt thereof, or L-glufosinate or a salt thereof.

40. Use of a compound of formula (IIIa):



(IIIa)

in the preparation of glufosinate or a salt thereof, or L-glufosinate or a salt thereof.

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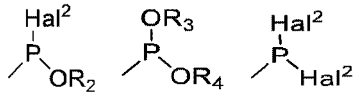
41. Use of a mixture in the preparation of glufosinate or a salt thereof, or L-glufosinate or a salt thereof,

wherein the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III); or a mixture comprising one or more compounds of formula (III), one or more compounds of formula (IV) and one or more compounds of formula (V),



(III) (IV) (V)

wherein Hal^2, R_2, R_3 and R_4 are as defined in any one of claims 1-13.

42. The use according to claim 41, characterized in that the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.05-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.05-1.1):1.

43. The use according to claim 42, characterized in that the mixture is a mixture comprising one or more compounds of formula (IV) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (IV) to the compounds of formula (III) is (0.9-1.1):1; or the mixture is a mixture comprising one or more compounds of formula (V) and one or more compounds of formula (III), and the molar ratio of the compounds of formula (V) to the compounds of formula (III) is (0.9-1.1):1.

44. The use according to any one of claims 41-43, characterized in that the compound of formula (IV) is diethyl methylphosphonite, and the compound of formula (V) is dichloro(methyl)phosphane.

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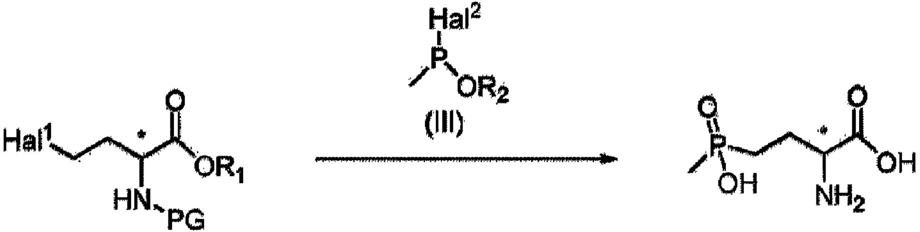

(II) (III) (I)