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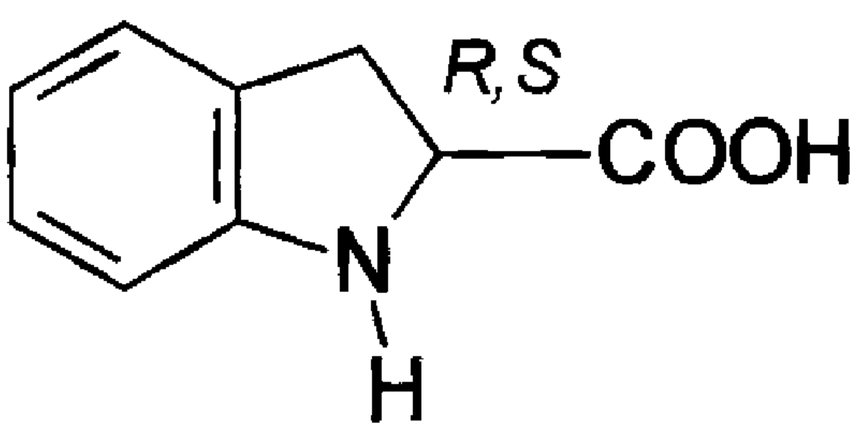
(71) Demandeur/Applicant:
APOTEX PHARMACHEM INC., CA

(72) Inventeurs/Inventors:
WANG, ZHI-XIAN, CA;
RAHEEM, MOHAMMED ABDUL, CA;
WEERATUNGA, GAMINI, CA

(74) Agent: IVOR M. HUGHES

(54) Titre : NOUVELLE METHODE DE PREPARATION D'ISOMERES OPTIQUES PURS DE L'ACIDE INDOLINE-2-CARBOXYLIQUE ET DE L'ACIDE N-ACETYL-INDOLINE-2-CARBOXYLIQUE

(54) Title: NEW PROCESSES FOR THE PREPARATION OF OPTICALLY PURE INDOLINE-2-CARBOXYLIC ACID AND N-ACETYL-INDOLINE-2-CARBOXYLIC ACID



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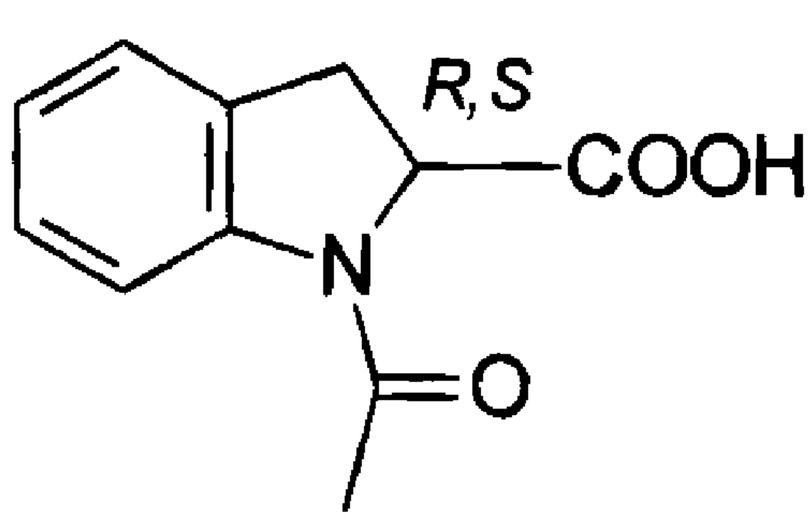

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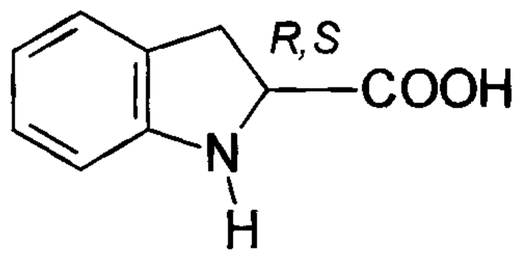
(57) Abrégé/Abstract:
Processes for: a) separating the enantiomers of indoline-2-carboxylic acid of formula 1 (see formula 1) comprising of: (i) combining the (R, S)-indoline-2-carboxylic acid with (1S)- or (1R)-10- camphorsulfonic acid as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (S)- or (R)-indoline-2-carboxylic acid with optically pure (1S)- or (1R)-10-camphorsulfonic acid; (ii) regenerating the (S)- or (R)-indoline-2-carboxylic acid from the crystallized diastereomeric salt by using a suitable base or basic ion-exchange resin; and b) for the optical resolution of N-acetyl-indoline-2-carboxylic acid of formula 2 (see formula 2) comprising of: (i) combining the (R, S)-N-acetyl-indoline-2-carboxylic acid with (S)- or (R)- phenylglycinol as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (S)- or (R)-N-acetyl-indoline-2-carboxylic acid with optically pure phenylglycinol; (ii) regenerating the (S)- or (R)-N-acetyl-indoline-2-carboxylic acid from the crystallized salt by using a suitable acid or acidic ion-exchange resin. The non-selected enantiomer may then be racemized and the process (a) or (b) repeated thus to obtain substantial conversion of the material to one enantiomer.

ABSTRACT

Processes for:

a) separating the enantiomers of indoline-2-carboxylic acid of formula **1**



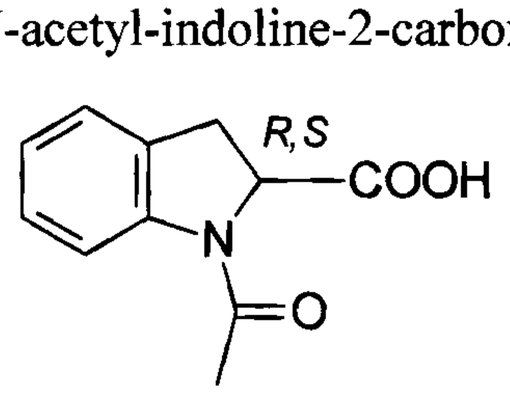
1

comprising of:

(i) combining the (*R*, *S*)-indoline-2-carboxylic acid with (1*S*)- or (1*R*)-10-camphorsulfonic acid as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-indoline-2-carboxylic acid with optically pure (1*S*)- or (1*R*)-10-camphorsulfonic acid;

(ii) regenerating the (*S*)- or (*R*)-indoline-2-carboxylic acid from the crystallized diastereomeric salt by using a suitable base or basic ion-exchange resin;

and b) for the optical resolution of N-acetyl-indoline-2-carboxylic acid of formula **2**



2

comprising of:

(i) combining the (*R*, *S*)-N-acetyl-indoline-2-carboxylic acid with (*S*)- or (*R*)-phenylglycinol as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-N-acetyl-indoline-2-carboxylic acid with optically pure phenylglycinol;

(ii) regenerating the (*S*)- or (*R*)-N-acetyl-indoline-2-carboxylic acid from the crystallized salt by using a suitable acid or acidic ion-exchange resin.

The non-selected enantiomer may then be racemized and the process (a) or (b) repeated thus to obtain substantial conversion of the material to one enantiomer.

TITLE OF THE INVENTION

NEW PROCESSES FOR THE PREPARATION OF OPTICALLY PURE INDOLINE-2-CARBOXYLIC ACID AND N-ACETYL- INDOLINE-2-CARBOXYLIC ACID

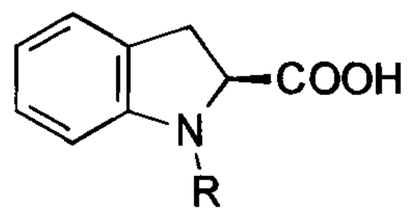
THIS APPLICATION IS A DIVISION OF CANADIAN APPLICATION SERIAL NO. 2,488,324 FILED ON NOVEMBER 22, 2004.

FIELD OF THE INVENTION

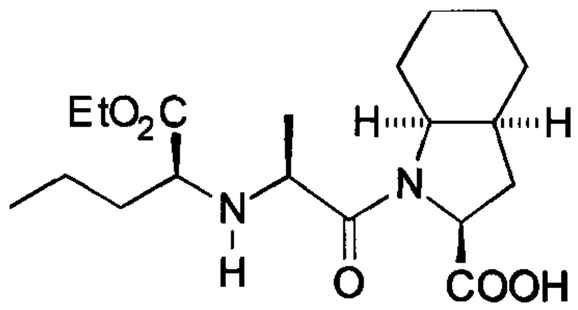
This invention relates to the production of optically pure indoline-2-carboxylic acid and N-acetyl-indoline-2-carboxylic acid.

BACKGROUND OF THE INVENTION

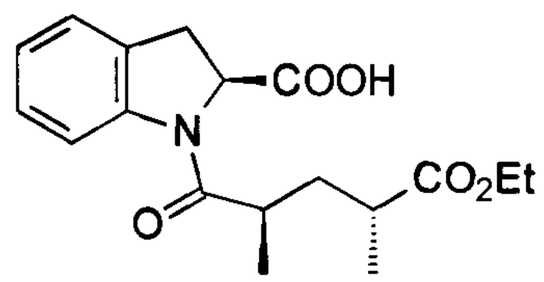
Optically pure indoline-2-carboxylic acid and N-acetyl-indoline-2-carboxylic acid are important intermediates in the synthesis of active pharmaceutical compounds. For example, (S)-indoline-2-carboxylic acid (**1**) and (S)-N-acetyl-indoline-2-carboxylic acid (**2**) are key intermediates in the synthesis of the ACE inhibitors perindopril **3** and pentopril **4**.



1. R = H
2. R = Ac



3. Perindopril



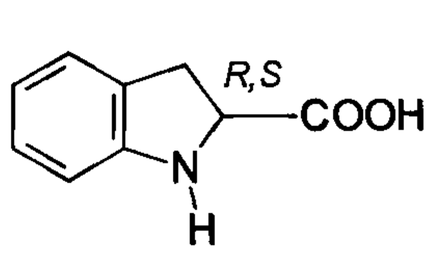
4. Pentopril

Optically pure indoline-2-carboxylic acid and N-acetyl-indoline-2-carboxylic acid were prepared via the prior art (M. Vincent, et al. *Tetrahedron Letters*, **1982**, *23*, 1677-1680,

US4954640) by the optical resolution of their racemates mixtures. For example, (S)-indoline-2-carboxylic acid was prepared by the resolution of racemic indoline-2-carboxylic acid using D-α-methylbenzylamine (M. Vincent, et al. *Tetrahedron Letters*, **1982**, *23*, 1677-1680, US4954640) or ephedrine (US4520205). Likewise, (S)-N-acetyl-indoline-2-carboxylic acid was prepared by the resolution of racemic acid with (-)-cinchonidine (US 4665087), α-amino-ε-caprolactam (EP 0171616) or N-substituted phenylalaninol (JP 61030572). Some of these resolving agents are expensive and not widely commercially available and the undesired enantiomers of indoline-2-carboxylic acid and N-acetyl-indoline-2-carboxylic acid produced in each case were not recovered. Optically pure indoline-2-carboxylic acid and N-acetyl-indoline-2-carboxylic acid also could be prepared by the cyclization of optically pure 2-bromophenylalanine derivatives (T. Ooi et al., *J. Amer. Chem. Soc.*, **2003**, *125*, 5139, S. Wagaw et al., *J. Amer. Chem. Soc.*, **1997**, *119*, 8451). However, the starting material, optically pure 2-bromophenylalanine derivatives, are not commercially available and are very difficult to synthesize. Also, the type of palladium catalyst used in the cyclization step is expensive and is not commercially available. Therefore, a new and efficient process for the preparation of optically pure indoline-2-carboxylic acid and derivatives overcoming the deficiencies of the prior art is required.

SUMMARY OF THE INVENTION

It is therefore one object of this invention to provide a new and efficient process for the resolution of (*R, S*)-indoline-2-carboxylic acid of formula **1** using a chiral acid and for producing new intermediate compounds.



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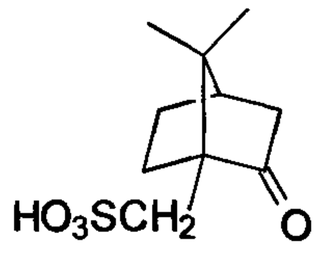
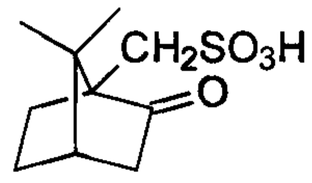


(1*S*)-**5**



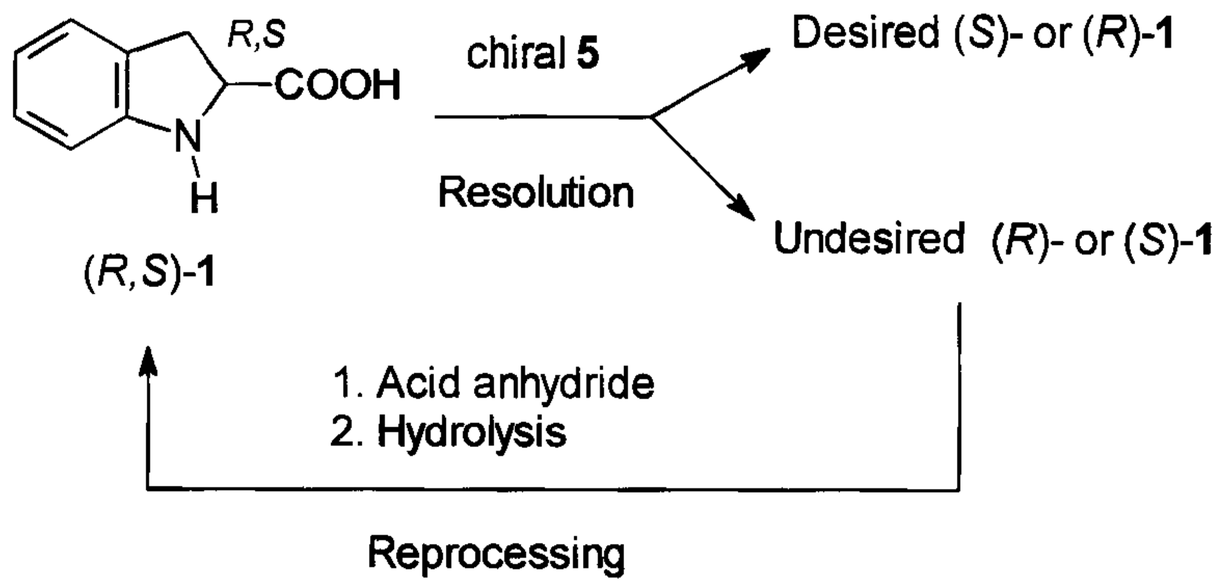
(1*R*)-**5**

We have discovered that (1*S*)- and (1*R*)-10-camphorsulfonic acids (**5**) are efficient resolving agents for **1**. Thus, (*S*) and (*R*)-**1** can be isolated as their diastereomeric salts with optically pure 10-camphorsulfonic acid.

It is another object of this invention to provide a process for reprocessing of the undesired enantiomer and then use of the resolution procedure. In this way, we are able to obtain almost complete conversion of the (*R, S*)-**1** to the desired enantiomer (*S*) or (*R*)-**1**.

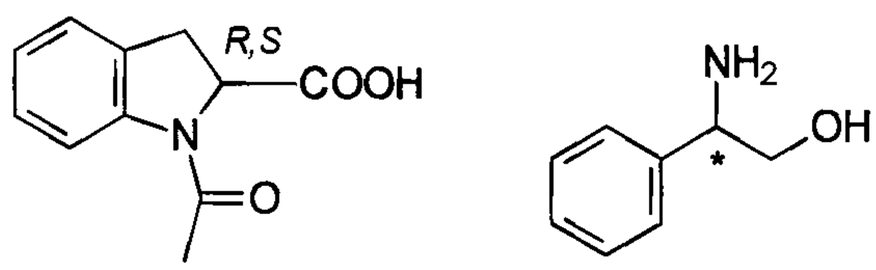
We have also found that treatment of the undesired enantiomer or enantiomeric mixture (enriched by one enantiomer) of **1** with an acid anhydride, preferably acetic anhydride, propionic anhydride or butyric anhydride, with or without a solvent, followed by hydrolysis furnished the (*R, S*)-**1**, which can be optically resolved by the procedure disclosed in the present invention as shown in Scheme 1.

Scheme 1.



It is also an object of the present invention to provide a commercial process for the resolution of (*R, S*)-N-acetyl-indoline-2-carboxylic acid of formula **2** using optically pure

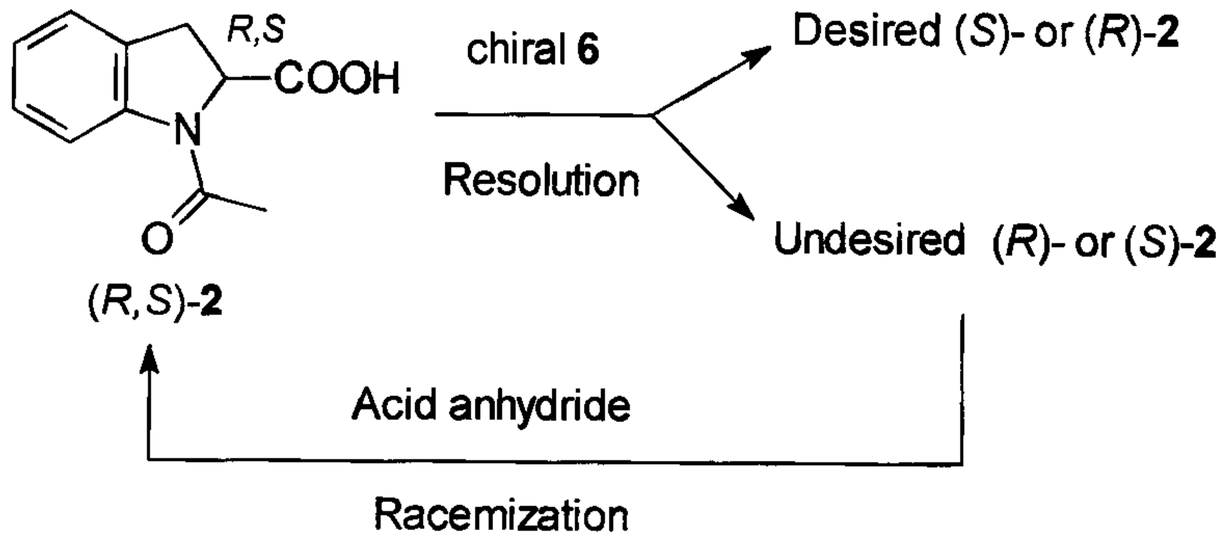
phenylglycinol (**6**) as a resolving agent and for producing new intermediate compounds. The optically pure phenylglycinol (**6**) is commercially available and inexpensive and can be easily produced by the reduction of optically pure phenylglycine.



2 **6**

It is another object of the present invention to provide a commercial process for racemization of the undesired enantiomer of **2** and then use of the resolution procedure. In this way, we are able to obtain almost complete conversion of the (*R, S*)-**2** to the desired enantiomer (*S*) or (*R*)-**2**. The undesired enantiomer or enantiomeric mixture (enriched by one enantiomer) of **2** is treated with an acid anhydride to furnish a mixture of (*R, S*)-**2**. The following are exemplary equations (scheme 2) according to the teachings of the present invention.

Scheme 2.



The instant invention has the following advantages:

1. The resolving reagents, optically pure **5** and **6**, are inexpensive and commercially available.

2. The racemization reaction conditions are mild, the acid anhydride used in the racemization steps is inexpensive and commercially available, and the recovery yields are good.

3. The potential recovery yield of desired enantiomer of **1** and **2** are more than 50% of starting material (*R, S*)-**1** and (*R, S*)-**2,** respectively.

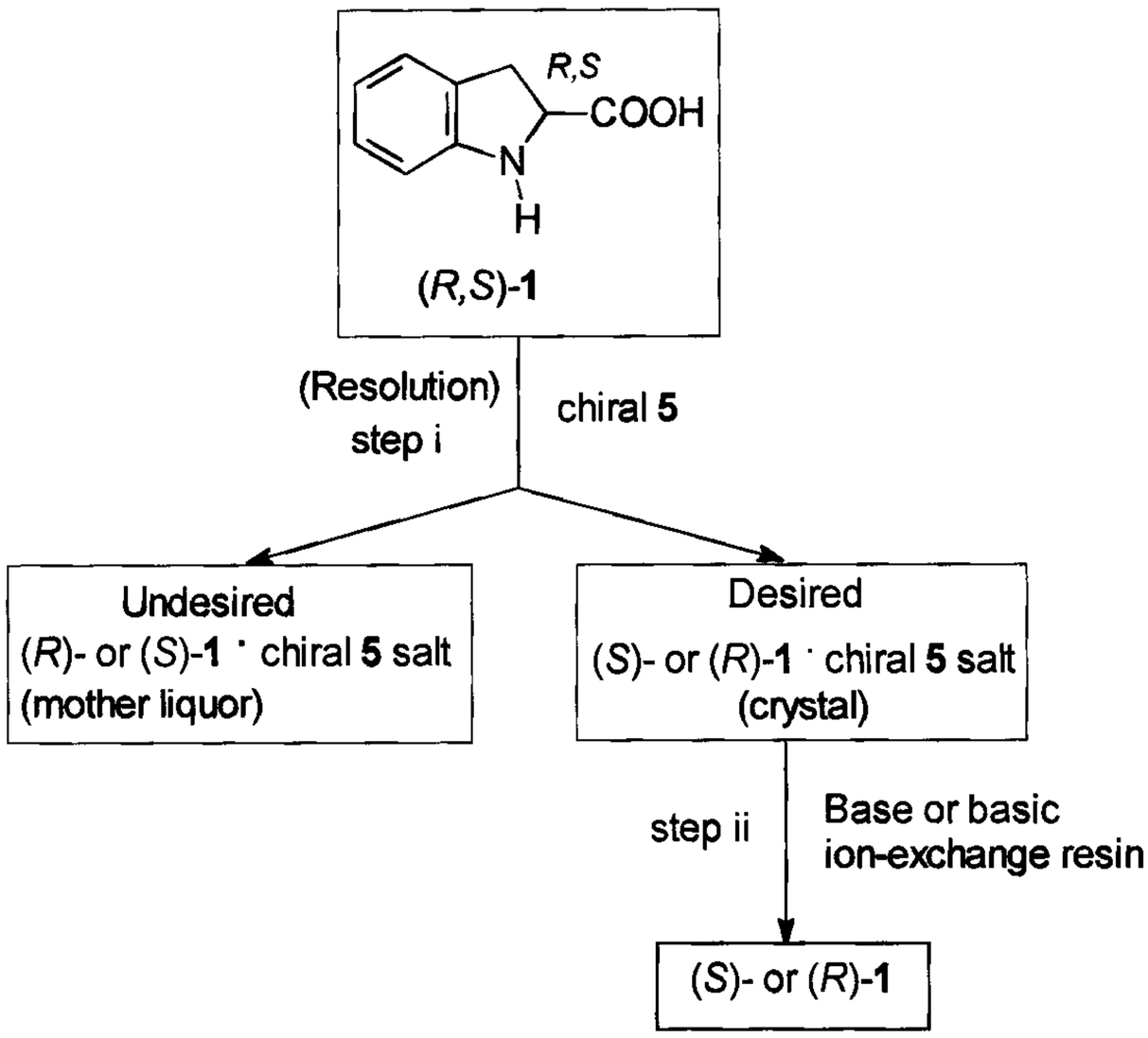
DETAILED DESCRIPTION OF ASPECTS OF THE INVENTION

According to an aspect of the present invention, a process for separating the enantiomers of indoline-2-carboxylic acid of formula **1** is provided. The process comprises:

(i) combining the (*R, S*)-**1** with (1*S*)- or (1*R*)-10-camphorsulfonic acid (**5**) as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-**1** with optically pure **5**;

(ii) regenerating the (*S*)- or (*R*)-**1** from the crystallized diastereomeric salt by using a suitable base or basic ion-exchange resin.

Scheme 3



Suitable resolution solvents include water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures, of which ethanol, isopropanol, water and their mixture are preferred.

The amount of resolving agent ranges from 0.5 to 1.1 equivalents relative to (*R*, *S*)-**1**.

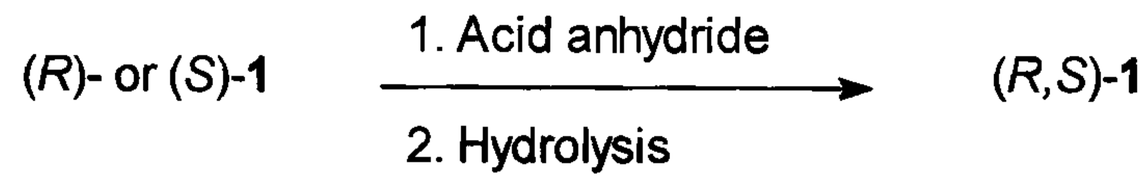
The crystallization can be carried out in the presence or absence of seed crystals of the diastereomeric salt of (*S*)- or (*R*)-**1** with optically pure **5**. The amount of seed is about 0.1 to 10 wt. % relative to the (*R*, *S*)-**1**, preferably the amount is 0.5 to 2.0 wt.%.

Regeneration of the resolved (*S*)- or (*R*)-**1** from the crystallized diastereomeric salts may be effected by treatment of the salt with a base or by use of an ion-exchange resin. Suitable bases include organic and inorganic bases, of which sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and triethylamine are preferred. The pH of the aqueous

solution during regeneration of the resolved indoline-2-carboxylic acid is between 1.5 to 4.0, preferably 2.0 to 3.0, the (*S*)- or (*R*)-**1** precipitates from the mixture and may be isolated by filtration.

Further, according to another aspect of the invention, a process is provided for the conversion of the enantiomer or enantiomeric mixture (enriched by one enantiomer) of indoline-2-carboxylic acid of formula **1** to the mixture of (*R*, *S*)-**1** by treating with an acid anhydride followed by hydrolysis and neutralization. The (*R*, *S*)-**1** can be subjected to the resolution process disclosed above.

Scheme 4



The acid anhydride used in racemization process includes C2-C16 acid anhydrides, of which acetic anhydride, propionic anhydride, butyric anhydride and benzoic anhydride are preferred. The racemization reaction is carried out in neat acid anhydride or with a co-solvent. The suitable solvents include alkylcarboxylic acids such as acetic acid, propionic acid and butyric acid, aromatic solvents such as toluene and xylenes, N,N-dialkylamides such as N,N-dimethylformamide, N,N-dimethylacetamide and 1-methyl-2-pyrrolidinone, and alkyl sulfoxides and sulfones such as dimethyl sulfoxide and sulfolane. The most preferred solvents are acetic acid and toluene. The amount of acid anhydride is about 1.0 to 5.0 equivalents relative to the indoline-2-carboxylic acid, more preferably the amount is about 2.0 to 3.0 equivalents. The reaction temperature is between 30 to 150 °C and the preferred temperature is 70-120 °C.

Hydrolysis may be carried out in the presence of an aqueous acid. The preferred acids are hydrochloric acid and sulfuric acid. The reaction temperature is between 30 to 150 °C, and the preferred temperature is 70-120 °C. After the hydrolysis, the reaction mixture is neutralized by the addition of a base. Suitable base includes organic and inorganic bases, of which sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and triethylamine are preferred. The pH of aqueous for neutralization is between 1.5 to 3.0, and the preferred pH range is 2.0 to 2.5. The mixture of (*R*, *S*)-**1** precipitates from the reaction mixture and may be isolated by filtration.

Further, according to another aspect of the invention, a process is provided for the preparation of (*S*)- or (*R*)-**1** via resolution of (*R*, *S*)-**1** and the recycling of the undesired enantiomer of **1**. The process comprises:

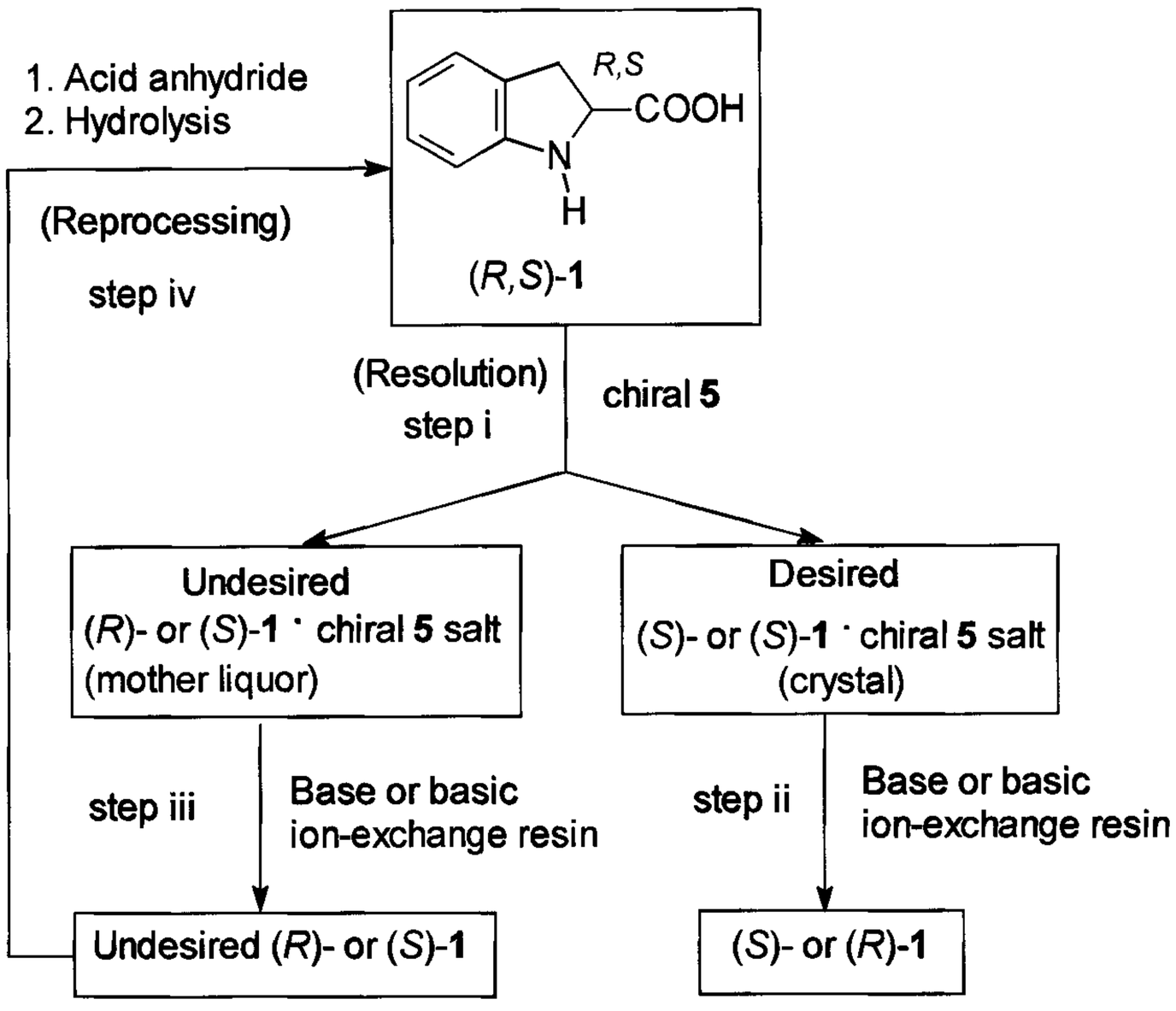
(i) combining the (*R*, *S*)-**1** with (1*S*)- or (1*R*)-10-camphorsulfonic acid (**5**) as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-**1** with optically pure **5**;

(ii) regenerating the (*S*)- or (*R*)-**1** from the crystallized salt by using a suitable base or basic ion-exchange resin;

(iii) optionally regenerating undesired (*R*)- or (*S*)-**1** or their mixture (enriched by one enantiomer) from the crystallization mother liquors; and

(iv) optionally recovering (*R*, *S*)-**1** via racemization of the undesired (*R*)- or (*S*)-**1** or their mixture (enriched by one enantiomer) with an acid anhydride followed by hydrolysis and neutralization and converting (*R*, *S*)-**1** to the desired (*S*)- or (*R*)-**1** through steps i) and ii).

Scheme 5



Suitable resolution solvents include water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures, of which ethanol, isopropanol, water and their mixture are preferred.

The amount of resolving agent ranges from 0.5 to 1.1 equivalents relative to (*R*, *S*)-**1**.

The crystallization can be carried out in the presence or absence of seed crystals of the diastereomeric salt of (*S*)- or (*R*)-**1** with optically pure **5**. The amount of seed is about 0.1 to 10 wt. % relative to the (*R*, *S*)-**1**, preferably the amount is 0.5 to 2.0 wt.%.

Regeneration of the resolved (*S*)- or (*R*)-**1** from the crystallized diastereomeric salts may be effected by treatment of the salt with a base or by use of an ion-exchange resin. Suitable bases include organic and inorganic bases, of which sodium hydroxide, potassium hydroxide,

sodium carbonate, potassium carbonate and triethylamine are preferred. The pH of the aqueous solution during regeneration of the resolved indoline-2-carboxylic acid is between 1.5 to 4.0, preferably 2.0 to 3.0, the (*S*)- or (*R*)-**1** precipitates from the mixture and is isolated by filtration.

Regeneration of the undesired (*R*)- or (*S*)-**1** or their mixture (enriched by one enantiomer) from the crystallization mother liquors can be carried out using the same procedure as regeneration of the desired (*S*)- or (*R*)-**1** from the crystallized salt.

The acid anhydride used in the racemization process includes C2-C16 acid anhydrides, of which acetic anhydride, propionic anhydride, butyric anhydride and benzoic anhydride are preferred. The racemization reaction is carried out in neat acid anhydride or with a co-solvent. The suitable solvents include C1 to C5 alkylcarboxylic acids such as acetic acid, propionic acid and butyric acid, aromatic solvents such as toluene and xylenes, N,N-dialkylamides such as N,N-dimethylformamide, N,N-dimethylacetamide and 1-methyl-2-pyrrolidinone, and alkyl sulfoxides and sulfones such as dimethyl sulfoxide and sulfolane. The most preferred solvents are acetic acid and toluene. The amount of acid anhydride is about 1.0 to 5.0 equivalents relative to the indoline-2-carboxylic acid, more preferably the amount is about 2.0 to 3.0 equivalents. The reaction temperature is between 30 to 150 °C and the preferred temperature is 70-120 °C.

Hydrolysis may be carried out in the presence of an aqueous acid. The preferred acids are hydrochloric acid and sulfuric acid. The reaction temperature is between 30 to 150 °C, and the preferred temperature is 70-120 °C. After the hydrolysis, the reaction mixture is neutralized by the addition of a base. Suitable bases include organic and inorganic bases, of which sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and triethylamine are preferred. The pH of aqueous phase during neutralization is between 1.5 to 3.0 and the

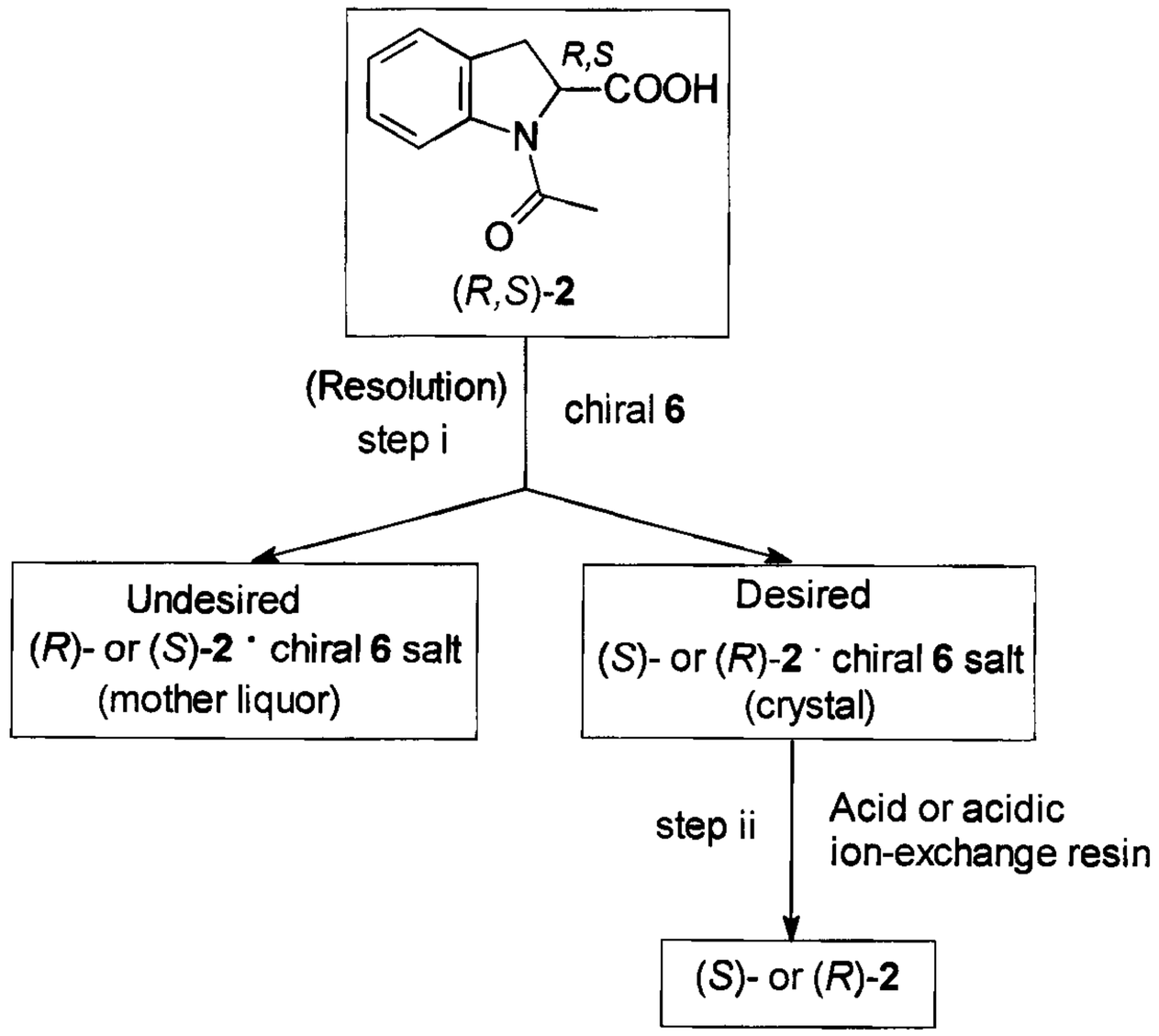
preferably 2.0 to 2.5. The mixture of (*R, S*)-**1** precipitates from the reaction mixture and may be isolated by filtration. The (*R, S*)-**1** can be resolved as disclosed above.

Further, according to another aspect of the invention, a process is provided for the resolution of N-acetyl-indoline-2-carboxylic acid of formula **2** using optically pure phenylglycinol **6** as a resolving agent. The process comprises:

(i) combining (*R*, *S*)-**2** with an optically pure (*R*)- or (*S*)-**6** as the resolving agent in a resolution solvent in the presence of or absence of a base and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-**2** with optically pure **6**;

(ii) regenerating the (*S*)- or (*R*)-**2** from the crystallized diastereomeric salt by using a suitable acid or acidic ion-exchange resin.

Scheme 6



Suitable resolution solvents include water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl

isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures, of which ethanol, isopropanol, water and their mixture are preferred.

The resolution may be carried out in the presence of or absence of a base. The base is selected from triethylamine, diisopropylethylamine, pyridine and the like. The amount of base ranges from 0.0 to 0.8 equivalents, preferable 0.0 to 0.5 equivalents relative to the (*R*, *S*)-**2**.

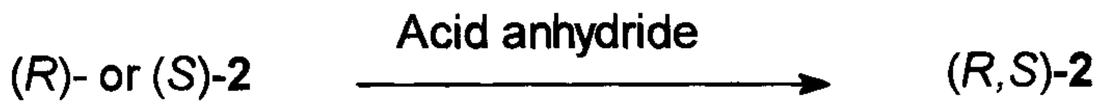
The crystallization can be carried out in the presence or absence of seed crystals of crystallized diastereomeric salt. The amount of seed is about 0.1 to 10 wt. % relative to the (*R*, *S*)-**2**, preferably the amount is 0.5 to 2.0 wt.%.

The amount of resolving reagent is between 0.5 to to 1.2 equivalents relative to the (*R*, *S*)-**2**.

Regeneration of the resolved (*S*)- or (*R*)-**2** from the crystallized diastereomeric salts may be effected by treatment of the salt with an acid or by use of an ion-exchange resin. Suitable acids include organic and inorganic acids, of which hydrochloric acid and sulfuric acid are preferred. The pH of the aqueous phase during regeneration of the resolved **2** is between 1.0 to 5.0 and preferably 1.0 to 3.0, the (*S*)- or (*R*)-**2** precipitates from the mixture and is isolated by filtration.

Further, according to another aspect of the invention, a process is provided for the conversion of the enantiomer or enantiomeric mixture (enriched by one enantiomer) of **2** or to mixture of (*R*, *S*)-**2** by treating with an acid anhydride. The (*R*, *S*)-**2** can be subjected to the resolution process disclosed in the present invention.

Scheme 7



Acid anhydride includes C2-C16 acid anhydride, of which acetic anhydride, propionic anhydride, butyric anhydride and benzoic anhydride are preferred and acetic anhydride is the most preferred. The racemization reaction is carried out in neat acid anhydride or with a co-solvent. The suitable solvents include alkylcarboxylic acids such as acetic acid, propionic acid and butyric acid, aromatic solvents such as toluene and xylenes, N,N-dialkylamides such as N,N-dimethylformamide, N,N-dimethylacetamide and 1-methyl-2-pyrrolidinone, and alkyl sulfoxides and sulfones such as dimethyl sulfoxide and sulfolane. The most preferred solvents are acetic acid and toluene. The amount of acid anhydride is about 1.0 to 5.0 equivalents relative to the N-acetyl-indoline-2-carboxylic acid, more preferably the amount is about 1.0 to 2.0 equivalents. The reaction temperature is between 30 to 150 °C, and the preferred temperature is 70-120 °C.

Further, according to another aspect of the invention, a process is provided for the resolution of N-acetyl-indoline-2-carboxylic acid of formula **2** and recycling the undesired enantiomer via a racemization process. The process comprises:

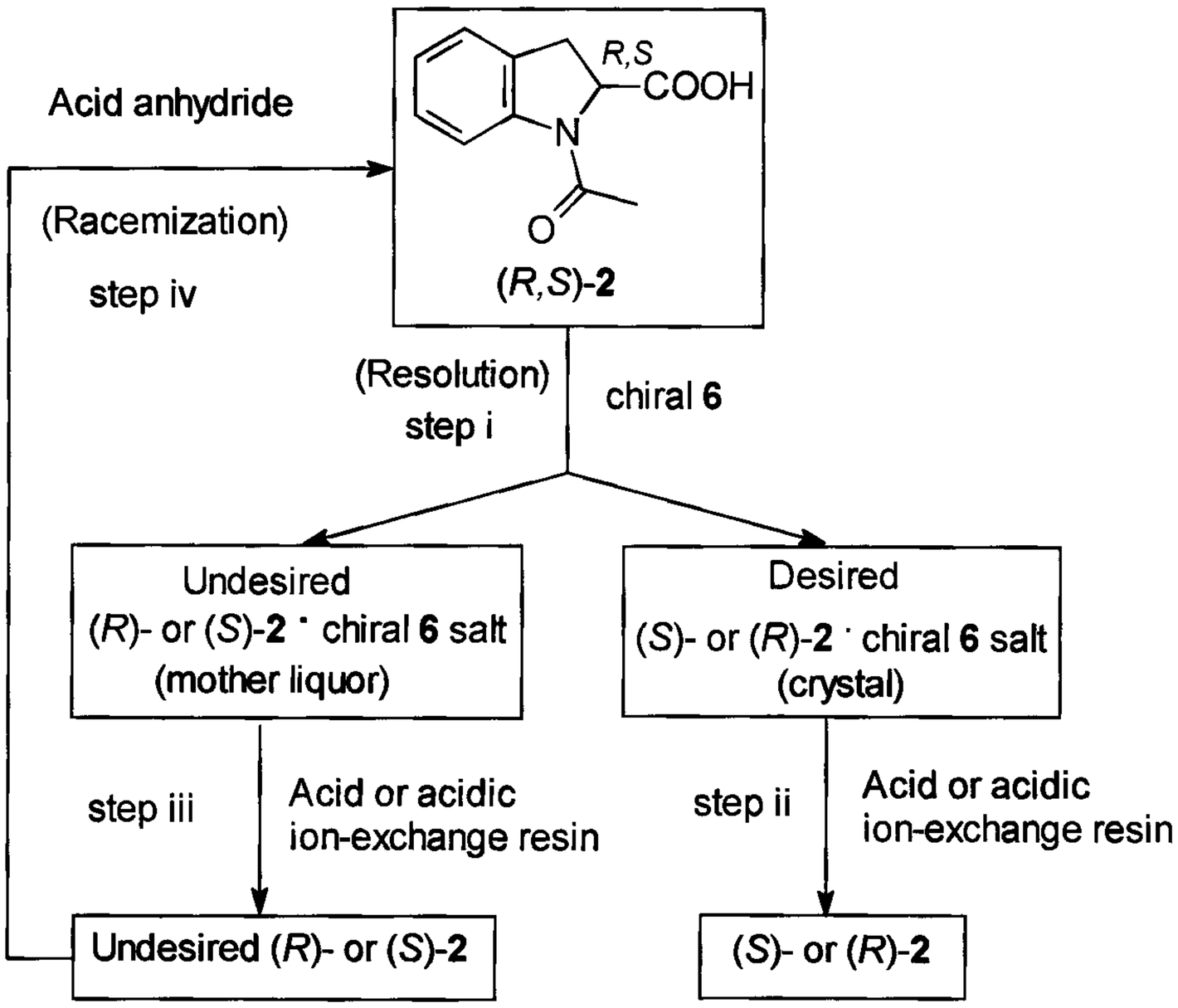
(i) combining (*R*, *S*)-**2** with optically pure (*R*)- or (*S*)-**6** as the resolving agent in a resolution solvent in the presence of or absence of a base and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-**2** with optically pure **6**;

(ii) regenerating the (*S*)- or (*R*)-**2** from the crystallized diastereomeric salt by using a suitable acid or acidic ion-exchange resin;

(iii) optionally regenerating undesired (*R*)- or (*S*)-**2** or their mixture (enriched by one enantiomer) from the crystallization mother liquors by using a suitable acid or acidic ion-exchange resin; and

(iv) optionally recovering and recycling (*R*, *S*)-**2** by racemization of undesired (*R*)- or (*S*)-**2** or their mixture obtained from step (iii) with an acid anhydride.

Scheme 8



Suitable resolution solvents include water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures, of which ethanol, isopropanol, water and their mixture are preferred.

The resolution is carried out in the presence of or absence of a base. The base is selected from triethylamine, diisopropylethylamine, pyridine and the like. The amount of base ranges from 0.0 to 0.8 equivalents, preferable 0.0 to 0.5 equivalents relative to the (*R*, *S*)-**2**.

The crystallization can be carried out in the presence or absence of seed crystals of

crystallized diastereomeric salt. The amount of seed is about 0.1 to 10 wt. % relative to the (*R*, *S*)-**2**, preferably the amount is 0.5 to 2.0 wt.%.

The amount of resolving reagent is between 0.5 to to 1.2 equivalents relative to the (*R*, *S*)-**2**.

Regeneration of the resolved (*S*)- or (*R*)-**2** from the crystallized diastereomeric salts may be effected by treatment of the salt with an acid or by use of an ion-exchange resin. Suitable acids include organic and inorganic acids, of which hydrochloric acid and sulfuric acid are preferred. The pH of the aqueous phase during regeneration of the resolved N-acetyl-indoline-2-carboxylic acid is between 1.0 to 5.0 and preferably 1.0 to 3.0, the (*S*)- or (*R*)-**2** precipitates from the mixture and is isolated by filtration.

Regeneration of the undesired (*R*)- or (*S*)-**2** or their mixture (enriched by one enantiomer) from the crystallization mother liquors can be carried out using the same procedure used for regeneration of (*S*)- or (*R*)-**2** from the crystallized salt.

The acid anhydride used in the racemization reaction includes C2-C16 acid anhydride, of which acetic anhydride, propionic anhydride, butyric anhydride and benzoic anhydride are preferred and acetic anhydride is the most preferred. The racemization reaction is carried out in neat acid anhydride or with a co-solvent. The suitable solvents include alkylcarboxylic acids such as acetic acid, propionic acid and butyric acid, aromatic solvents such as toluene and xylenes, N,N-dialkylamides such as N,N-dimethylformamide, N,N-dimethylacetamide and 1-methyl-2-pyrrolidinone, and alkyl sulfoxides and sulfones such as dimethyl sulfoxide and sulfolane. The most preferred solvents are acetic acid and toluene. The amount of acid anhydride is about 1.0 to 5.0 equivalents relative to the N-acetyl-indoline-2-carboxylic acid,

more preferably the amount is about 1.0 to 2.0 equivalents. The reaction temperature is between 30 to 150 °C, and the preferred temperature is 70-120 °C.

The following non-limiting embodiments of the invention further illustrate the manner of carrying out the inventive processes described herein and the inventive intermediate compounds made thereby.

EXAMPLE 1

The mixture of (*R*, *S*)-indoline-2-carboxylic acid (8.2 g), (1*S*)-10-camphorsulfonic acid (11.2g) in isopropanol-ethanol (1:1 v/v) (80 mL) was heated to 40 °C to give a clear solution. (*S*)-Indoline-2-carboxylic acid (1*S*)-10-camphorsulfonic acid salt (0.1 g) was added as seeds and the mixture was cooled slowly to 20 °C to give a white suspension. After stirred at 20 °C for 2 h, the mixture was filtered and washed with isopropanol to give white solid (6.9 g). The solid was pulped from isopropanol to give (*S*)-indoline-2-carboxylic acid (1*S*)-10-camphorsulfonic acid salt as a white solid (5.7 g), $[\alpha]_D^{20} = -5.2$ (c 0.5, methanol).

The suspension of the above salt (5.15 g) in water (25 mL) was cooled to 0-5 °C and treated with 15% NaOH solution to pH 2.9. The resulting suspension was filtered and rinsed with water. The solid was dried under vacuum to give 1.9 g of (*S*)-indoline-2-carboxylic acid, $[\alpha]_D^{20} = -113.2$ (c 1, 1N HCl). A sample was converted to N-acetyl-indoline-2-carboxylic acid and analysis by chiral HPLC and showed 99.8% *S* enantiomer.

EXAMPLE 2

The mixture of (*S*)-indoline-2-carboxylic acid (16.4 g), acetic anhydride (26.0g) in acetic acid (33 mL) was heated to 100 °C and stirred for 3 h. Water (80 mL) and 32% hydrochloric acid

(17.1 g) was added and the mixture was stirred at 100 °C for 5 h. The solution was concentrated under vacuum to 30 mL, diluted with water (50 mL) and cooled to 0-5 °C. The pH of the solution was adjusted to 2.0-2.5 by the addition of 25% sodium hydroxide solution. After being stirred at 0-5 °C for 1 h, the resulting suspension was filtered and washed with water. The solid was dried under vacuum to give 14.9 g of (*RS*)-indoline-2-carboxylic acid, $[\alpha]_D^{20} = 0$ (c 1, 1N HCl).

EXAMPLE 3

Prepared as Example 2, starting from (*S*)-indoline-2-carboxylic acid (16.4 g) and propionic anhydride (30.0g) to give 15.1 g of (*RS*)-indoline-2-carboxylic acid, $[\alpha]_D^{20} = 0$ (c 1, 1N HCl).

EXAMPLE 4

The mixture of (*R*, *S*)-N-Acetyl-indoline-2-carboxylic acid (50 g), (*R*)-phenylglycinol (20 g) in isopropanol (500 mL) and water (45 mL) was heated to 75-80 °C to give a clear solution. The solution was slowly cooled to 15-20 °C and stirred for 2 h. The resulting suspension was filtered and washed with isopropanol. The solid was blended with isopropanol (250 mL) and water (25 mL) to give 25 g (*S*)-N-Acetyl-indoline-2-carboxylic acid (*R*)-phenylglycinol salt as a white solid. $[\alpha]_D^{20} = -106.8$ (c 0.5, methanol), Chiral HPLC 99.4% *S* enantiomer.

The salt (20 g) was mixed with water (80 mL) and cooled to 0-5 °C. pH of the mixture was adjusted to 1.5 to 2.0 by the addition of hydrochloric acid. After being stirred at 0-5 °C for 1 h, the suspension was filtered and rinsed with water. The solid was dried under vacuum to give

11.7 g (*S*)-N-Acetyl-indoline-2-carboxylic acid as a white solid. $[\alpha]_D^{20}$ = -128.4 (c 1.0, ethanol), Chiral HPLC 99.9% *S* enantiomer.

The combined resolution and crystallization mother liquor were evaporated under vacuum and the residue suspended in water (150 mL). pH of the mixture was adjusted to 1.5 to 2.0 by the addition of hydrochloric acid. After being stirred at 0-5 °C for 1 h, the mixture was filtered, washed with water and dried to give 31 g light yellow solid. Chiral HPLC showed 70% *R* enantiomer. 30 g of this solid was stirred with acetic acid (90 mL) and acetic anhydride (16.54 g) at 100 °C for 3 h. After cooled to 20 °C, the mixture was diluted with water (180 mL) and the mixture was filtered, washed with water and dried to give 29 g (*R*, *S*)- N-Acetyl-indoline-2-carboxylic acid. $[\alpha]_D^{20}$ = 0 (c 1, methanol).

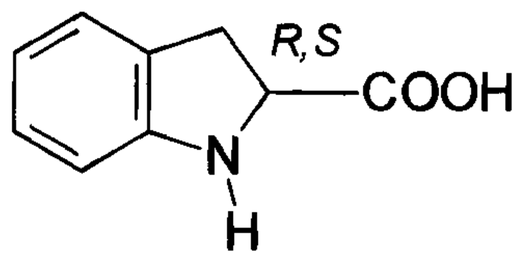
EXAMPLE 5

The mixture of (*R*)-N-acetyl-indoline-2-carboxylic acid (50 g), acetic anhydride (27.36 g) in acetic acid (150 mL) was heated to 100 °C and stirred for 3 h. It was then cooled to 20 °C, water (250 mL) was added and the mixture was stirred at 0-5 °C for 2 h. The suspension was filtered and washed with water. The solid was dried under vacuum to give 46.7 g of (*R*, *S*)–N–acetyl-indoline-2-carboxylic acid, $[\alpha]_D^{20}$ = 0 (c 1, 1N HCl).

While the foregoing embodiments provide detailed description of preferred embodiments of the invention, it is to be understood that these are illustrative only of the principles of the invention and not limiting. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A process for separating the enantiomers of indoline-2-carboxylic acid of formula **1**



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comprising of:

(i) combining the (*R*, *S*)-indoline-2-carboxylic acid with (1*S*)- or (1*R*)-10-camphorsulfonic acid as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-indoline-2-carboxylic acid with optically pure (1*S*)- or (1*R*)-10-camphorsulfonic acid;

(ii) regenerating the (*S*)- or (*R*)-indoline-2-carboxylic acid from the crystallized diastereomeric salt by using a suitable base or basic ion-exchange resin.

2. The process according to claim 1 wherein the resolution solvent is selected from a group consisting of water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures.

3. The process according to claim 1 wherein the resolution solvent is isopropanol, ethanol, water and their mixture.

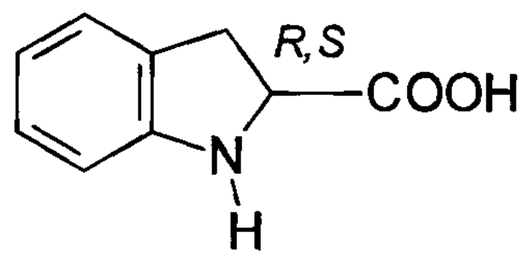
4. The process according to claim 1 wherein (1*S*)-10-camphorsulfonic acid is used as the resolving agent.

5. The process according to claim 1 wherein (1*R*)-10-camphorsulfonic acid is used as the resolving agent.

6. A process for the conversion of the enantiomer or enantiomeric mixture (enriched by one enantiomer) of indoline-2-carboxylic acid of formula **1** to the mixture of (*R*, *S*)-indoline-2-carboxylic acid via racemization with an acid anhydride followed by hydrolysis and neutralization.

7. The process according to claim 6 wherein acid anhydride is selected from C2-C16 acid anhydrides.

8. A process for separating the enantiomers of indoline-2-carboxylic acid of formula **1** and recycling of the undesired enantiomer comprising of:



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(i) combining the (*R*, *S*)- indoline-2-carboxylic acid with (1*S*)- or (1*R*)-10-camphorsulfonic acid as the resolving agent in a resolution solvent and crystallizing from the said mixture the diastereomeric salt of (*S*)- or (*R*)-indoline-2-carboxylic acid with optically pure (1*S*)- or (1*R*)-10-camphorsulfonic acid; and

(ii) regenerating the (*S*)- or (*R*)-indoline-2-carboxylic acid from the crystallized diastereomeric salt by using a suitable base or basic ion-exchange resin;

9. The process of claim 8 wherein the undesired (*R*)- or (*S*)-indoline-2-carboxylic acid or their mixture (enriched by one enantiomer) is regenerated from the crystallization mother liquors.

10. The process of claim 9 wherein the (*R*, *S*)-indoline-2-carboxylic acid is recovered via racemization of the undesired (*R*)- or (*S*)-indoline-2-carboxylic acid or their mixture (enriched by one enantiomer) with an acid anhydride followed by hydrolysis and neutralization and converting (*R*, *S*)-indoline-2-carboxylic acid to the desired (*S*)- or (*R*)-indoline-2-carboxylic acid through steps i) and ii).

11. The process according to claim 8 wherein the resolution solvent is selected from a group consisting of water, C1 to C7 alcohols such as methanol, ethanol, isopropanol and butanols, C3 to C7 ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone, C2 to C7 nitriles such as acetonitrile, C3 to C7 esters such as ethyl acetate and methyl acetate, and their mixtures.

12. The process according to claim 8 wherein the resolution solvent is isopropanol, ethanol, water and their mixture.

13. The process according to claim 8 wherein (1*S*)-10-camphorsulfonic acid is used as the resolving agent.

14. The process according to claim 8 wherein (1*R*)-10-camphorsulfonic acid is used as the resolving agent.

15. The process according to claim 6 wherein acid anhydride is selected from C2-C16 acid anhydrides.

16. (*S*)-Indoline-2-carboxylic acid (1*S*)-10-camphorsulfonic acid salt.

17. (*S*)-Indoline-2-carboxylic acid (1*R*)-10-camphorsulfonic acid salt.

18. (*R*)-Indoline-2-carboxylic acid (1*R*)-10-camphorsulfonic acid salt.

19. (*R*)-Indoline-2-carboxylic acid (1*S*)-10-camphorsulfonic acid salt.

20. (*S*)-N-Acetyl-indoline-2-carboxylic acid (*R*)-phenylglycinol salt.

21. (*S*)-N-Acetyl-indoline-2-carboxylic acid (*S*)-phenylglycinol salt.

22. (*R*)-N-Acetyl-indoline-2-carboxylic acid (*S*)-phenylglycinol salt.

23. (*S*)-N-Acetyl-indoline-2-carboxylic acid (*R*)-phenylglycinol salt.