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(54) Title: PROCESS FOR THE PREPARATION OF (S)-(+)-CLOPIDOGREL ON A SOLID-PHASE

(57) Abstract: The present invention relates to a process for preparing S-(+)-clopidogrel using a solid-phase reaction, and more particularly, to a process for preparing S-(+)- clopidogrel represented by the following formula 1 with high optical and chemical purity by carrying out a series of reactions and purifications more simply by a solid- phase synthetic approach using a polymer support.



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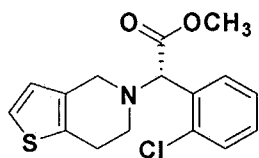
PROCESS FOR THE PREPARATION OF (S)-(+)-CLOPIDOGREL ON A SOLID-PHASE

Technical Field

5 The present invention relates to a process for preparing S-(+)-clopidogrel using a solid-phase reaction, and more particularly, to a process for preparing S-(+)-clopidogrel represented by the following formula 1 with high optical and chemical purity by carrying out a series of reactions and purifications more simply by a solid-phase synthetic approach using a polymer support.

Background Art

[Formula 1]



The chemical name of the S-(+)-clopidogrel represented by formula 1 is methyl (+)-(S)- α -(o-chlorophenyl)6,7-dihydrothieno[3,2-a]pyridine-5-(4H)-acetate and has
15 been known as an effective therapeutic agent for treating vascular system diseases including peripheral arterial diseases, such as cerebral apoplexy, thrombus, embolus, etc., and coronary arterial diseases, such as myocardial infarction, angina pectoris, etc., as it shows a strong inhibitory activity against platelet aggregation and an

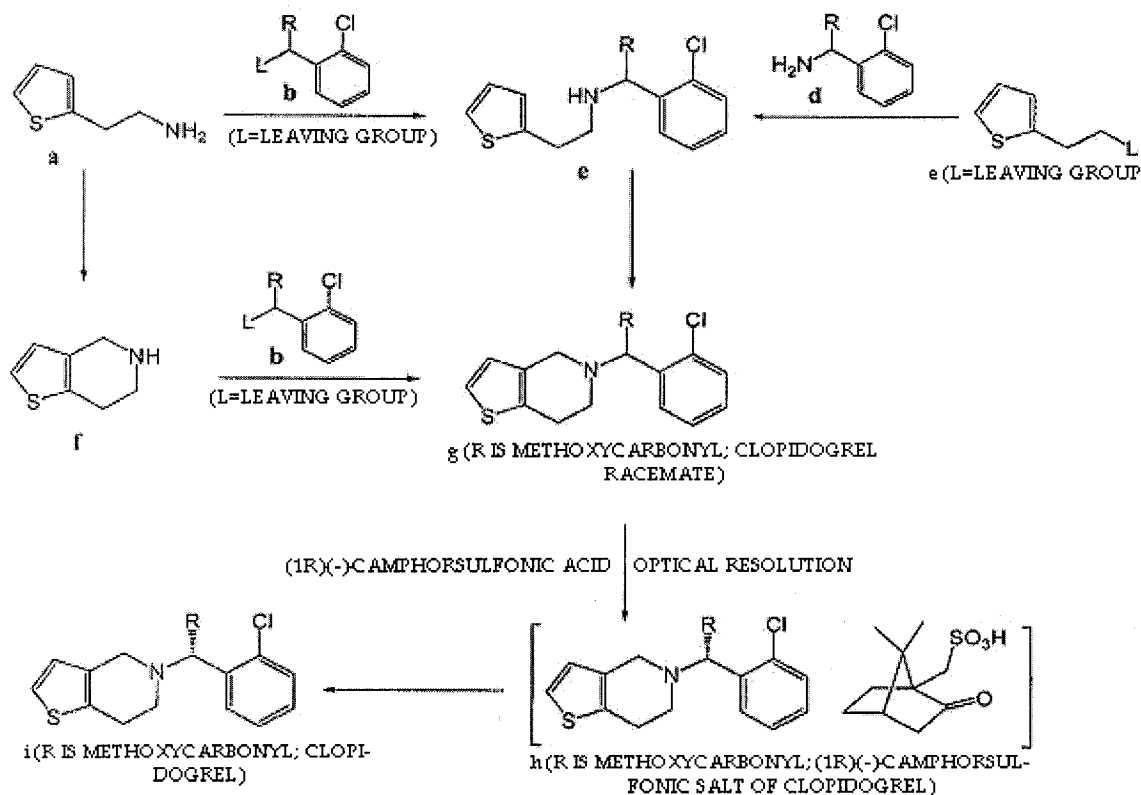
antithrombotic activity.

According to recent research, it has been reported that the S-(+)-clopidogrel is a very effective agent inhibiting platelet aggregation as it shows a strong effect of inhibiting the platelet aggregation in with a small dose compared with aspirin and it
5 minimizes the toxic effects to be given on the gastrointestinal tract.

The S-(+)-clopidogrel is commercially available with the name of "Plavix®" and the tablet of this product contains approximately 98mg of S-(+)-clopidogrel hydrogen sulphate and approximately 75mg of S-(+)-clopidogrel base as an active ingredient.

10 As general processes for the preparation of clopidogrel, the preparation processes disclosed in the U.S. Patent Nos. 4,529,596, 4,847,265 and 5,204,469 can be summarized and expressed by the following scheme 1:

[Scheme 1]



According to the processes of the conventional methods disclosed in scheme 1, there is required an optical resolution process comprising forming a diastereomeric salt (h) by reacting a clopidogrel racemate (g) with an optically active acid, obtaining a pure diastereomeric salt of a dextrorotatory (R) optical isomer containing no levorotatory (L) optical isomers by recrystallization, and subsequently removing the optically active acid to prepare S-(+)-clopidogrel as an optically pure dextrorotatory isomer.

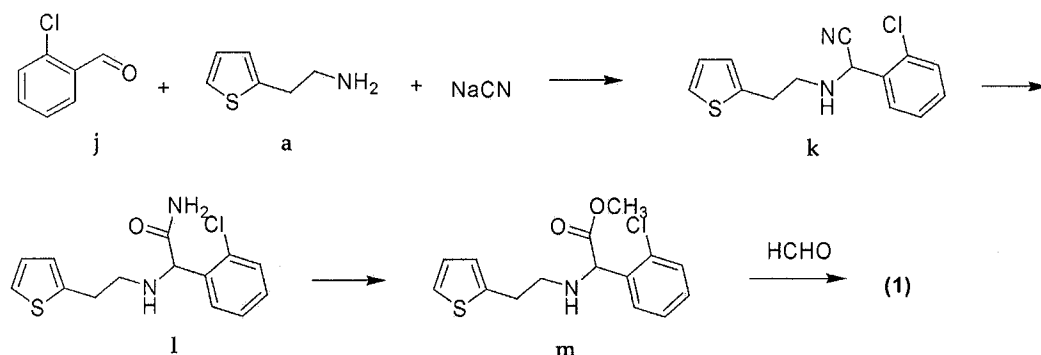
U.S. Patent No. 4,847,265 discloses an optical resolution method for the

preparation of S-(+)-clopidogrel using a (1R)-(-)-camphorsulfonic acid as an optically active acid. International Patent Publication No. WO 98/051689 discloses a process for preparing S-(+)-clopidogrel by performing an optical resolution and subsequent reactions from a compound of formula (e) in scheme 1, wherein R is a nitrile, carboxamide, or carboxylic acid. Moreover, International Patent Publication No. WO 02/059128 has disclosed a process for preparing S-(+)-clopidogrel by carrying out an optical resolution and subsequent reactions of a compound from formula (g) in scheme 1, wherein R is a nitrile, carboxamide, or carboxylic acid.

As described above, the known processes for the preparation of S-(+)-clopidogrel may involve out the optical resolution inevitably in a specific step of the successive preparation processes. However, the optical resolution process of the clopidogrel racemate and an intermediate thereof is very disadvantageous environmentally or economically since it is unavoidable that, as for the levorotatory isomer, at least 50% of the intermediate is wasted. Moreover, in performing the optical resolution process to obtain an optical isomer with high purity, it is essential to repeat the purification process such as recrystallization several times, and thus the resulting yield becomes usually reduced.

International Patent Publication No. WO 98/051689 discloses a method to overcome the above drawbacks, which can be summarized and expressed by the following scheme 2:

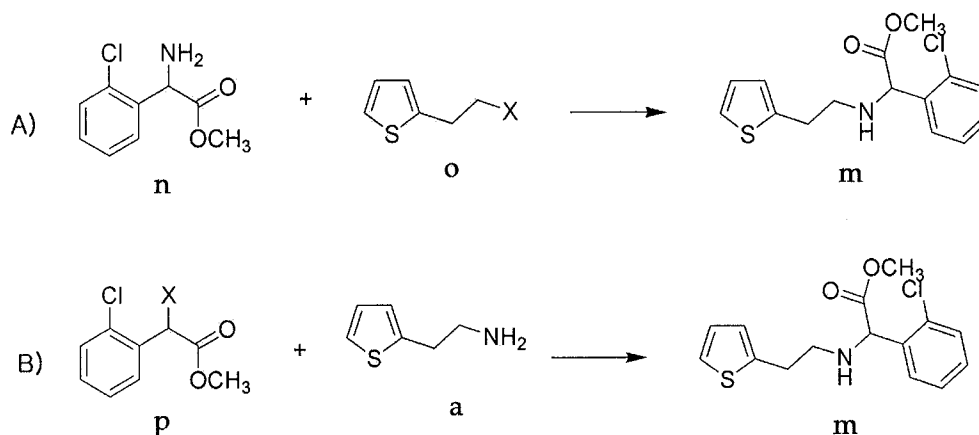
[Scheme 2]



In the conventional process according to scheme 2, 2-(2-thienyl)-ethanamine of formula (a) in scheme 2 is reacted with o-chlorobenzaldehyde of formula (j) in scheme 2 and sodium cyanide. The resulting nitrile compound of formula (k) in scheme 2 is converted into an amide compound corresponding to formula (l) in scheme 2 and then converted into a methyl ester compound of formula (m) in scheme 2. An intermediate (m) that is an appropriate form used for the synthesis of clopidogrel may be prepared by reacting with an optically active acid through an optical separation process of amide (l) or ester (m). Finally, the optical isomer of formula (m) in scheme 2 is subjected to cyclization with formaldehyde in an acidic medium, thus preparing clopidogrel.

As another conventional process, the process disclosed in European Patent No. 0466569 can be summarized and expressed by the following scheme 3:

[Scheme 3]

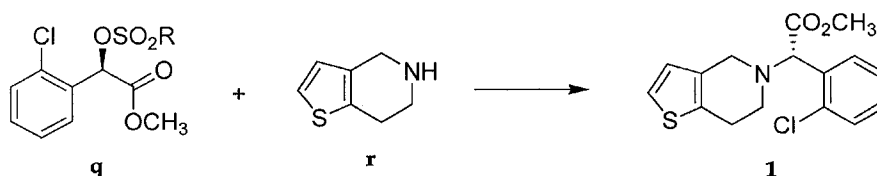


wherein X is a halogen or a sulfonate group.

In the conventional process according to scheme 3, methyl 2-amino-(2-chlorophenyl)acetate of formula (n) in scheme 3 is reacted with 2-(2-thienyl)ethanol derivative of formula (o) in scheme 3 to prepare an intermediate of formula (m) in scheme 3 (Process A), or methyl 2-halo-(2-chlorophenyl)acetate of formula (p) in scheme 3 is reacted with 2-(2-thienyl)-ethanamine of formula (a) in scheme 3 to obtain an intermediate of formula (m) in scheme 3 (Process B).

Moreover, International Patent Publication No. WO 99/018110 discloses a process for preparing clopidogrel by a reaction between tetrahydrothienopyridine (r) and (R)-2-chloromandelic acid ester with a sulfonate leaving group (q) as expressed by the following scheme 4.

[Scheme 4]



However, the conventional process according to scheme 4 using 4,5,6,7-tetrahydro[3,2-c]thienopyridine of formula (r) in scheme 4 has a drawback that it is difficult to be purified by crystallization since it has a low melting point and is readily dissolved in an organic solvent.

As described above, the conventional processes for the preparation of clopidogrel have numerous drawbacks to be improved.

Accordingly, the inventors of the present invention has developed a novel process for the synthesis of clopidogrel, to which a preparation process of a novel concept significantly different from the organic synthesis process of clopidogrel known so far, i.e., a solid-phase reaction using a polymer support is introduced, and completed the present invention.

Accordingly, an object of the present invention is to provide a process for preparing S-(+)-clopidogrel with high optical and chemical purity by carrying out a reaction process and a purification process more simply by a solid-phase reaction.

Disclosure

As represented by the following scheme 5, the present invention provides a process for preparing S-(+)-clopidogrel, which includes the steps of:

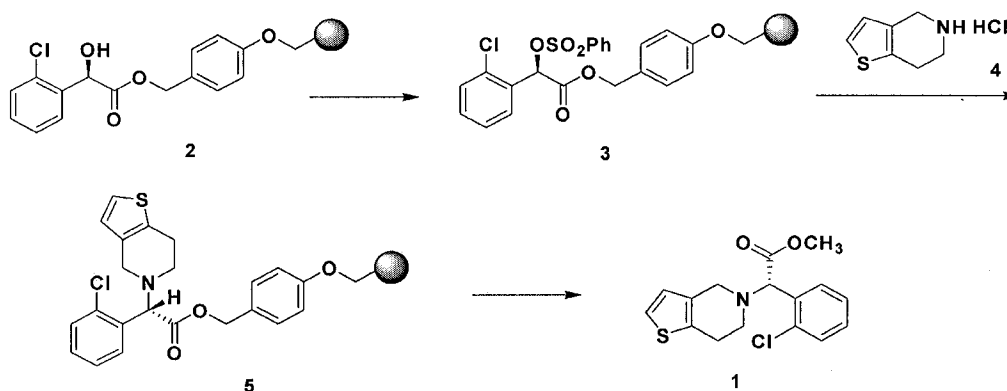
(1) preparing a sulfonylated resin represented by the following formula 3 by

5 sulfonylating a hydroxy resin represented by the following formula 2;

(2) preparing a resin compound represented by the following formula 5 by reacting the sulfonylated resin represented by formula 3 with a 4,5,6,7-tetrahydro[3,2-c]thienopyridine hydrochloride salt represented by the following formula 4; and

(3) preparing an S-(+)-clopidogrel represented by the following formula 1 by
10 separating the resin compound represented by formula 5 from a polymer support and by a methyl esterification reaction.

[Scheme 5]



wherein  represents a polymer support for solid-phase reaction.

Hereinafter, the present invention will be described in more detail.

The present invention is directed to a process for preparing (S)-(+)-clopidogrel represented by formula 1 efficiently by carrying out a solid-phase reaction.

The process for preparing (S)-(+)-clopidogrel in accordance with the present invention is carried out by the solid-phase reaction using a polymer support. The conventional solid-phase reaction has advantages that (1) the purification process is simplified as residual reactants and reaction by-products can be readily removed by resin washing; (2) the preparation process can be automated as multi-step reaction processes can be made easily and successive reactions are available; (3) it can deal with the compounds, not causing damage to the environment, as toxic or harmful compounds are bonded to resin.

The solid-phase support used in the solid-phase reaction in accordance with the present invention is the one generally used in solid-phase combinatorial chemistry synthesis techniques. Polymer supports having a skeleton structure such as polystyrene-divinylbenzene, methacrylic acid- dimethylacrylamide, hydroxyl methacrylic acid, etc. may be used; however, the present invention does not impose restrictions on the selection of the polymer supports. The polymer supports used in the solid-phase reaction of the present invention may be exemplified by Merrifield resin, Wang resin or a derivative thereof.

Any organic solvent swelling the polymer supports may be applicable to the

solid-phase reaction in accordance with the present invention. For example, dimethylsulfoxide (DMSO), tetrahydrofuran (THF), dimethylformamide (DMF), methanol (MeOH), dichloromethane (CH₂Cl₂), etc. may be used as the reaction solvent.

It was possible to readily obtain a target compound with high purity even if the purification of the solid-phase reaction in accordance with the present invention was carried out by a simple method such as filtration and washing. Water and organic solvents might be available as the solvent used in the filtration, and the by-products and the residual reactants produced should be removed as much as possible.

The preparation process in accordance with the present invention will be described in more detail by the respective steps.

Step (1) is directed to a process of sulfonylating the hydroxy resin represented by formula 2. The sulfonylation reaction is carried out by using a conventional sulfonylation agent. More specifically, a benzenesulfonyl chloride may be used as the sulfonylation agent and the sulfonylation reaction may be carried out under the condition of using a base catalyst such as dimethylaminopyridine (DMAP) or triethylamine. Moreover, the above sulfonylation reaction may be performed at a temperature range of -20 to 30°C and preferably at room temperature.

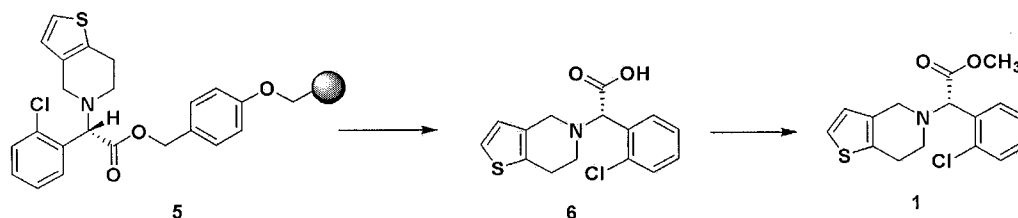
Step (2) is directed to a process of bonding the sulfonylated resin represented by formula 3 to the 4,5,6,7-tetrahydro[3,2-c]thienopyridine hydrochloride salt represented by formula 4. The present invention is characterized by using the compound

represented by formula 4 in the form of a hydrochloride salt. Accordingly, the present invention provides a method of solving the drawbacks of having difficulty in purification associated with the same thienopyridine in the form of a free base since its melting point is low and the poor crystalline property. The bonding reaction may be performed at a temperature range of -20 to 30°C and preferably at room temperature. Moreover, the bonding reaction may be carried out under the condition of using a base catalyst such as dimethylaminopyridine (DMAP) or triethylamine, if necessary.

Step (3) is directed to a process of preparing an S-(+)-clopidogrel represented by formula 1 in accordance with the present invention by separating the compound represented by formula 5 from the polymer support through a methyl esterification reaction.

In carrying out the preparation process in accordance with the present invention, step (3) may be carried out in a two-step process for preparing the (S)-(+)-clopidogrel represented by formula 1 as depicted in the following scheme 6. That is, it is possible to prepare the (S)-(+)-clopidogrel represented by the following formula 1 by separating a compound represented by the following formula 5 from the polymer support to obtain a compound represented by the following formula 6 and then performing the methyl esterification reaction.

[Scheme 6]



wherein  represents a polymer support for solid-phase reaction.

The separation process from the polymer support can be readily performed by using an organic acid such as trifluoroacetic acid (TFA) and the like at a temperature range of -20 to 30°C and preferably at room temperature. Besides, the compound represented by formula 6 can be readily separated from the polymer support by various methods well-known in the art.

The compound represented by formula 6 separated from the polymer support is subjected to the methyl esterification reaction to obtain the (S)-(+)-clopidogrel in accordance with the present invention. That is, the methyl esterification reaction may be carried out by reacting the compound represented by formula 6 with methanol under an acidic condition, where an organic acid such as thionyl chloride and the like is used 1.0 to 2.0 equivalents, at a temperature range of 40 to 80°C, preferably, at a reflux temperature.

Moreover, in carrying out the preparation process in accordance with the present invention, step (3) may be carried out in a one-step process, where the separation from the polymer support and the methyl esterification reaction are

simultaneously performed by reacting the compound represented by formula 5 with an alkali metal alkoxide, thus preparing the (S)-(+)-clopidogrel represented by formula 1 in accordance with the present invention.

That is, the (S)-(+)-clopidogrel represented by formula 1 can be prepared by heating and stirring the compound represented by formula 5 with the alkali metal alkoxide of 0.1 to 1 equivalent at reflux. Here, the reaction solvent used in the present invention may be a general organic solvent and preferably a mixed solvent of methanol and tetrahydrofuran mixed in a volume ratio of 1:5 to 5:1. In case of a reaction in which the alkali metal alkoxide is used, the separation and the methyl esterification can be achieved by a single reaction. Accordingly, it may be a very useful process in terms of process simplification and an industrial point of view as it can prevent the corrosion of the reactor caused by using acidic materials such as trifluoroacetic acid or thionyl chloride.

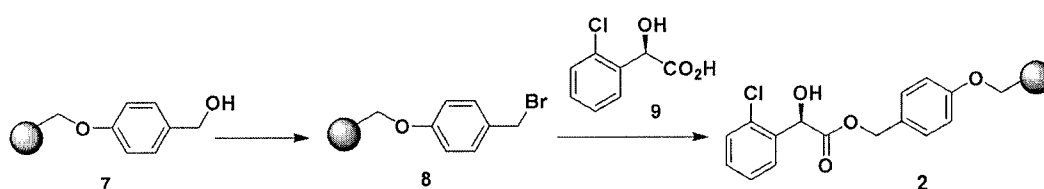
Moreover, the polymer supports exhausted in the separation process can be recovered and recycled by an appropriate treatment.

Meanwhile, the compound represented by formula 2 used as a starting material in the preparation process in accordance with the present invention may be prepared by a conventional method.

For example, as depicted in the following scheme 7, in case of using a Wang resin as a polymer support, the compound represented by the following formula 2 used

as a starting material can be prepared by brominating a hydroxyl group of a Wang resin end represented by the following formula 7 to form a brominated resin represented by the following formula 8 and then bonding the brominated resin with a (R)-2-chloromandelic acid represented by the following formula 9.

[Scheme 7]



wherein  represents a polymer support for solid-phase reaction.

Moreover, in case of using a Merrifield resin, the compound represented by formula 2 can be prepared by bonding the (R)-2-chloromandelic acid represented by formula 9 directly to the resin represented by formula 8.

Furthermore, in performing the preparation process by the solid-phase reaction in accordance with the present invention, the respective polymer reactions can be confirmed by FT-IR readily and qualitatively. In addition, the chemical structure of the compound can be analyzed and confirmed by NMR and mass spectrum after the compound is separated from the polymer support and then purified and separated by column chromatography.

The (S)-(+)-clopidogrel represented by formula 1 prepared by the solid-phase reaction as described above may be prepared as a pharmaceutically acceptable salt by a general method. That is, it is possible to form pharmaceutically acceptable salts along

with organic or inorganic acids such as hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, lactic acid, maleic acid, succinic acid, tartaric acid and the like, or prepare pharmaceutically acceptable salts by reacting with alkali metal ions, such as sodium, potassium, etc., or with ammonium ions.

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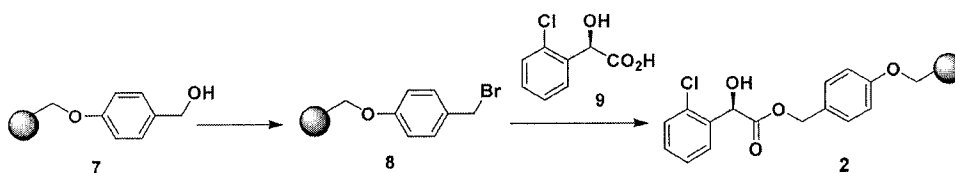
Best Mode

The present invention as described above will be described in more detail based on the following examples; however, the present invention is not limited thereto.

10 Examples: Synthesis of (S)-(+)-clopidogrel by successive solid-phase reactions

Example 1: Synthesis of (S)-(+)-clopidogrel by successive reactions including four steps

(1) Synthesis of hydroxy resin of formula 2



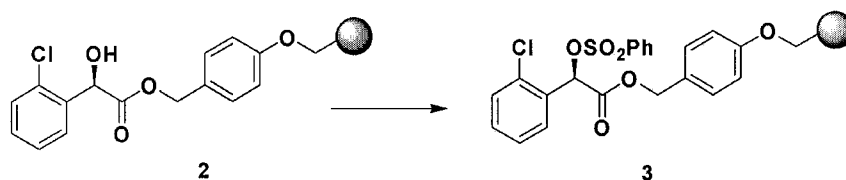
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Wang resin (7; 0.87 mmol/g, 1 g, 0.87 mmol) and triphenylphosphine (0.684 g, 2.7 mmol) were placed into a 50 mL flask, dichloromethane (20 mL) was added and then shaken for 10 minutes. Then, bromine (Br₂; 0.134 mL, 2.61 mmol) was slowly added thereto. After reaction at room temperature for 5 hours, the resin was washed

with each 50 mL of water, water:DMF (1:1), DMF, MeOH, MeOH:CH₂Cl₂ (1:1) and CH₂Cl₂ (two times) in the sequential order and then dried under vacuum at room temperature to obtain a brominated resin (8).

The brominated resin (8) obtained as above, (R)-2-chloromandelic acid (9; 647.3 mg, 3.48 mmol) and cesium carbonate (1.28 g, 3.92 mmol) were placed into a 50 mL flask, diluted with DMF (40 mL) and then shaken at room temperature for 4 hours. The resin was washed with each 50 mL of water, water:DMF (1:1), DMF, MeOH, MeOH:CH₂Cl₂ (1:1) and CH₂Cl₂ (two times) in the sequential order and then dried under vacuum at room temperature to obtain hydroxy resin (2). The hydroxy resin (2) was used in the following reaction without any purification process and the formation of the compound was confirmed by FT-IR (FT-IR: 3514, 1736 cm⁻¹).

(2) Synthesis of sulfonylated resin of formula 3

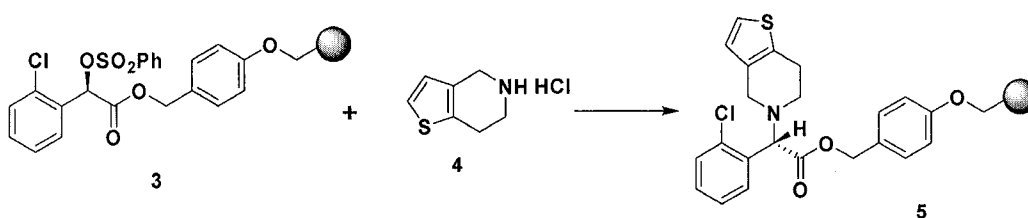


The hydroxy resin (2) obtained in the above step was placed into a 50 mL flask and diluted with CH₂Cl₂ (30 mL). Then, benzenesulfonyl chloride (0.23 mL, 1.74 mmol), triethylamine (0.36 mL, 2.61 mmol), dimethylaminopyridine (DMAP; 53 mg) were added and shaken at room temperature for 12 hours. The resin was washed with each 50 mL of water, water:DMF (1:1), DMF, MeOH, MeOH:CH₂Cl₂ (1:1) and

CH₂Cl₂ (two times) in the sequential order and then dried under vacuum at room temperature to obtain sulfonylated resin (3). The sulfonylated resin (3) was used in the following reaction without any purification process and the formation of the compound was confirmed by FT-IR (FT-IR: 1439, 1375 cm⁻¹).

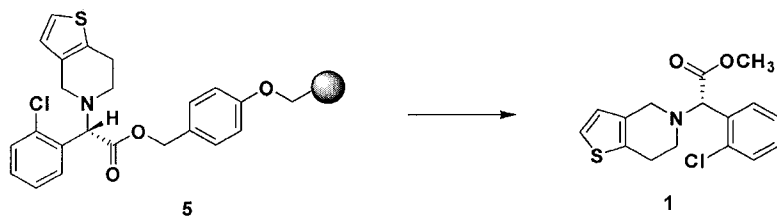
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3) Synthesis of resin compound of formula 5



4,5,6,7-tetrahydrothieno(3,2-c)pyridine hydrogen chloride (4; 454 mL, 2.61 mmol) was placed into a 50 mL flask, CH₂Cl₂ solvent (30 mL) and triethylamine (0.73 mL, 5.22 mmol) were added and then shaken for 30 minutes. The sulfonylated resin (3) obtained in the above step was added thereto and shaken at room temperature for 12 hours. The resin was washed with each 50 mL of water, water:DMF (1:1), DMF, MeOH, MeOH:CH₂Cl₂ (1:1) and CH₂Cl₂ (2 times) in the sequential order and then dried under vacuum at room temperature to obtain resin compound (5). The resin compound (5) was used in the following reaction without any purification process and the formation of the compound was confirmed by FT-IR (FT-IR: 1095, 1016 cm⁻¹).

(4) Synthesis of (S)-(+)-clopidogrel of formula 1



20 mL of a mixed solution of THF:MeOH (4:1) was placed into a 50 mL flask, the resin compound (5) obtained in the above step and 20 mg of sodium methoxide were added and then heated at reflux for 6 hours. The resulting solution was cooled to room temperature and 10 mL of ammonium chloride solution was added thereto.

The resulting solution was extracted with CH_2Cl_2 (20 mL $\times$ 2 times) and then dried with Na_2SO_4 . After filtered and concentrated under reduced pressure, the resultant was passed through a small amount of silica gel column and washed with ethyl acetate:*n*-hexane (1:6). Then, the resultant was dried under vacuum at room temperature to obtain 162 mg of (S)-(+)-clopidogrel (1) as a pale yellow oil.

Yield of the successive reactions (1) to (4) of example 1 58%; optical purity 98 %e.e. (HPLC); ^1H NMR (300 MHz, CDCl_3) δ 7.68-7.70 (m, 1H), 7.38-7.44 (m, 1H), 7.27-7.30 (m, 2H), 7.06 (d, 1H, $J = 5.1$ Hz), 6.67 (d, 1H, $J = 5.1$ Hz), 4.92 (s, 1H), 3.72(s, 3H), 3.61-3.79 (m, 2H), 2.88 (brs, 4H).

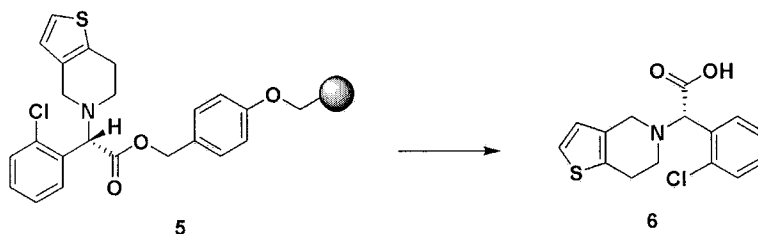
The optical purity of the (S)-(+)-clopidogrel synthesized in the above step was measured by chiral HPLC and the HPLC conditions applied to the separation are as follows:

- Column: Ultron ES-OVM (Ovomucoid product), 150 $\times$ 4.6 mm, 5.0 mm

- Flow rate: 1 mL/min.
- Detection wavelength: 220 nm
- Eluate: dibasic sodium phosphate buffer solution (20 nM, pH 7)/acetonitrile (80/20, v/v)
- Sample: dissolved in a mixed solution of 0.1 mg/mL of the dibasic sodium phosphate buffer solution (20 nM, pH 7)/acetonitrile (80/20, v/v)

Example 2: Synthesis of (S)-(+)-clopidogrel by successive reactions including five steps

(5) Synthesis of compound of formula 6



The reaction was continuously carried out following the successive reactions (1) to (3) of example 1.

That is, the resin compound (5) obtained in step (3) of example 1 was placed into a 50 mL flask, 20 mL of trifluoroacetic acid (TFA):CH₂Cl₂ (1:4) was added and then shaken at room temperature at 6 hours. The resin was filtered under reduced pressure and washed with MeOH (10 mL x 2 times) and CH₂Cl₂ (10 mL x 2 times). The filtrate was concentrated under reduced pressure, passed through a small amount of silica gel

column and then washed with MeOH:CH₂Cl₂ (1:19) several times. The resulting filtrate was concentrated under reduced pressure, crystallized by adding diethyl ether and *n*-hexane and then dried under vacuum to obtain 165 mg of compound (6) as a white solid.

5 Yield of the continuous reactions (1) to (4) of example 1, 62%; optical purity, 98 %e.e. (HPLC); ¹H NMR (300 MHz, CDCl₃) δ 10.61 (brs, 1H), 7.81-7.84 (m, 1H), 7.37-7.40 (m, 1H), 7.20-7.31 (m, 2H), 7.16 (d, 1H, *J* = 5.1 Hz), 6.66 (d, 1H, *J* = 5.1 Hz), 5.29 (s, 1H), 4.17-4.30 (m, 2H), 3.44-3.64 (m, 2H), 3.06 (brs, 2H).

10 The optical purity of the compound of formula 6 synthesized as above was measured by chiral HPLC and the HPLC conditions applied to the separation are as follows:

- Column: Ultron ES-OVM (Ovomucoid product), 150 × 4.6 mm, 5.0 mm
- Flow rate: 1 mL/min
- Detection wavelength: 220 nm
- 15 - Eluate: methanol/dibasic sodium phosphate buffer solution (2 nM, pH 7.5) (5/95, v/v)
- Sample: dissolved in a mixed solution of 0.1 mg/mL of the methanol/dibasic sodium phosphate buffer solution (2 nM, pH 7.5) (5/95, v/v) and added 10mL thereto.

20 (6) Synthesis of (S)-(+)-clopidogrel of formula 1

The compound (6; 40 mg, 0.13 mmol) obtained in the above step was dissolved in 2 mL of MeOH. Thionyl chloride (0.013 mL, 0.16 mmol) was added to the resulting solution and then stirred at 70°C for 6 hours. After cooled to room temperature, the resulting solution was concentrated under reduced pressure and then 20 mL of water was added thereto. After adding 5% NaHCO₃ (4 mL), the resulting solution was extracted with CH₂Cl₂ (20 mL) and then dried using Na₂SO₄. After filtered and concentrated under reduced pressure, the resultant was passed through a small amount of silica gel column and washed with ethyl acetate:*n*-hexane (1:6). Then, the resultant was dried under vacuum at room temperature to obtain 35 mg of (S)-(+)-clopidogrel (1) as a pale yellow oil.

Yield 84%; optical purity 98 %e.e. (HPLC); ¹H NMR (300 MHz, CDCl₃) δ 7.66-7.70 (m, 1H), 7.37-7.44 (m, 1H), 7.27-7.31 (m, 2H), 7.07 (d, 1H, *J* = 5.1 Hz), 6.66 (d, 1H, *J* = 5.1 Hz), 4.92 (s, 1H), 3.73(s, 3H), 3.60-3.80 (m, 2H), 2.89 (brs, 4H).

The optical purity of the (S)-(+)-clopidogrel synthesized as above was measured by chiral HPLC and the HPLC conditions applied to the separation are the same as step (4) of example 1.

Industrial Applicability

As described in detail above, the preparation process by the solid-phase reaction in accordance with the present invention is very useful as the purification

process is conveniently carried out and the (S)-(+)-clopidogrel can be prepared with high optical and chemical purity.

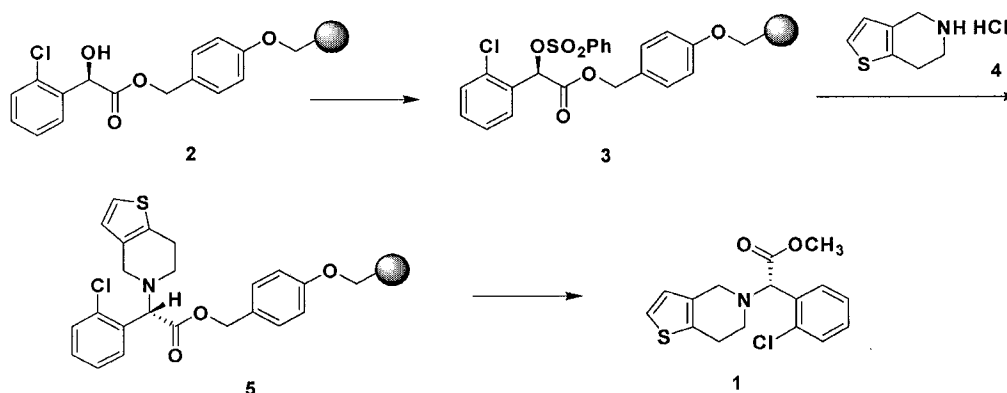
CLAIMS

1. A process for preparing (S)-(+)-clopidogrel comprising the steps of:

(1) preparing a sulfonylated resin represented by the following formula 3 by sulfonylating a hydroxy resin represented by the following formula 2;

(2) preparing a resin compound represented by the following formula 5 by reacting the sulfonylated resin represented by formula 3 with a 4,5,6,7-tetrahydro[3,2-c]thienopyridine hydrochloride salt represented by the following formula 4; and

(3) preparing an S-(+)-clopidogrel represented by the following formula 1 by separating the resin compound represented by formula 5 from a polymer support through a methyl esterification reaction.

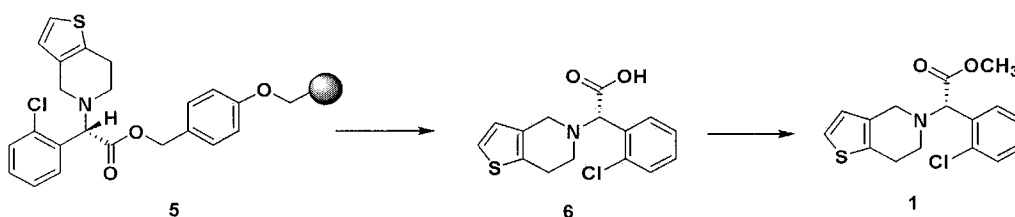


wherein  represents a polymer support for solid-phase reaction.

2. In claim 1, the polymer support for solid-phase reaction has a polymer skeleton structure selected from the group consisting of polystyrene-divinylbenzene, methacrylic acid- dimethylacrylamide and hydroxyl methacrylic acid.

3. In claim 1, the polymer support for solid-phase reaction is Wang resin, Merrifield resin or a derivative thereof.

4. In claim 1, in step (3), the (S)-(+)-clopidogrel represented by the following
 5 formula 1 is prepared by separating a compound represented by the following
 formula 5 from a polymer support to obtain a compound represented by the following
 formula 6 and then by carrying out a methyl esterification reaction:



wherein  represents a polymer support for solid-phase reaction.

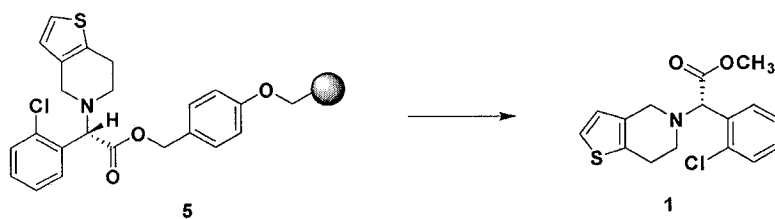
5. In claim 4, the separation is carried out using an organic acid.

6. In claim 5, the organic acid is a trifluoroacetic acid.

7. In claim 4, the methyl esterification reaction is carried out by reacting the
 15 compound represented by formula 6 with methanol under an acidic condition.

8. In claim 1, in step (3), the (S)-(+)-clopidogrel represented by the following

formula 1 is directly prepared by carrying out separation and methyl esterification reactions simultaneously by refluxing a compound represented by the following formula 5 with an alkali metal alkoxide:

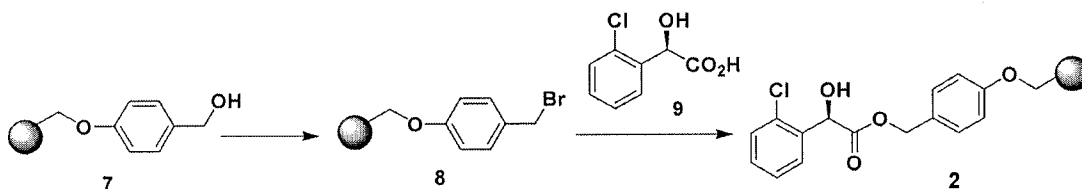


wherein represents a polymer support for solid-phase reaction.

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9. In claim 8, the alkali metal alkoxide is a sodium methoxide.

10. In claim 1, the hydroxy resin represented by formula 2 is prepared by brominating a hydroxyl group of a Wang resin end represented by the following formula 7 to form a brominated resin represented by the following formula 8 and then subjected to a bonding reaction with a (R)-2-chloromandelic acid represented by the following formula 9:



wherein represents a polymer support for solid-phase reaction.

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11. In claim 1, the hydroxy resin represented by formula 2 is prepared by

bonding the (R)-2-chloromandelic acid represented by formula 9 directly to the resin represented by formula 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2006/005602**A. CLASSIFICATION OF SUBJECT MATTER***C07D 495/04(2006.01)i, C07D 513/08(2006.01)i, C07D 498/02(2006.01)i, A61P 7/02(2006.01)i, A61P 9/10(2006.01)i*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and Applications for Inventions since 1975Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN(REGISTRY, CA), eKIPASS, PubMed (keywords: Clopidogrel, Solid Phase, Enantiomer)**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002-0177712 A1 (CADILA HEALTHCARE LTD.) 28 November 2002 See pages 1,2 and claim 1.	1-11
A	US 6,800,759 B2 (TEVA PHARMACEUTICAL INDUSTRIES LTD.) 5 October 2004 See abstract and claims 1-10.	1-11
A	WO 05-063708 A2 (SUBRAMANIAM, H. et al.) 02 November 2004 See pages 4-6.	1-11
A	WO 03-066637 A1 (EGIS, G. et al.) 14 August 2003 See claims 1-10.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

26 MARCH 2007 (26.03.2007)

Date of mailing of the international search report

26 MARCH 2007 (26.03.2007)

Name and mailing address of the ISA/KR

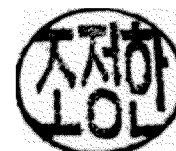
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2006/005602

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