Title: PROCESS FOR HIGH YIELD PRODUCTION OF CLOPIDOGREL BY RACEMIZATION OF RESIDUAL LIQUID

Abstract: The present invention relates to a process for preparing S-(+)-clopidogrel in high yield by means of racemization of filtrate, and particularly to a process comprising (a) conducting an optical resolution by converting racemic carboxylic acid of clopidogrel to diastereomer salt using (+)-cinchonine, (b) preparing carboxylic acid of S-(+)-clopidogrel by extraction using an appropriate solvent under an acidic condition, (c) preparing optically pure S-(+)-clopidogrel by reacting the carboxylic acid of S-(+)-clopidogrel with methanol, wherein a filtrate, which remains after collecting the diastereomer salt as solid precipitates, is recycled after being converted to a racemic carboxylic acid of clopidogrel via racemization under a basic condition, thereby maximizing the yield of S-(+)-clopidogrel.
[DESCRIPTION]

[I Invention Title]

Process for high yield production of clopidogrel by racemization of residual liquid

[Technical Field]

The present invention relates to a process for preparing S-(+)-clopidogrel in high yield by means of racemization of a filtrate, and particularly to a process comprising (a) conducting an optical resolution by converting racemic carboxylic acid of clopidogrel to diastereomer salt using (+)-cinchonine, (b) preparing carboxylic acid of S-(+)-clopidogrel by extraction using an appropriate solvent under an acidic condition, (c) preparing optically pure S-(+)-clopidogrel by reacting the carboxylic acid of S-(+)-clopidogrel with methanol, wherein a filtrate, which remains after collecting the diastereomer salt as solid precipitates, is recycled after being converted to racemic carboxylic acid of clopidogrel via racemization in the presence of a basic solution, thereby maximizing the yield of S-(+)-clopidogrel.

[Formula 1]

S-(+)-clopidogrel of Formula 1, i.e., methyl (+)-(S)-α-(o-chlorophenyl)-6,7-dihydrothieno[3,2-a]pyridine-5(4H)-acetate, has a strong inhibitory activity against
platelet aggregation and anti-thrombotic activity and thus has been known useful for the treatment of peripheral arterial diseases (e.g., cerebral apoplexy, thrombus, embolus, etc.) and coronary arterial diseases (e.g., myocardial infarction, angina pectoris, etc.).

According to recent researches, it has been shown that S-(+)-clopidogrel is a very effective agent having a better inhibiting platelet aggregation than aspirin even with a less amount while its toxic effect on the gastrointestinal tract is much reduced as compared to that of aspirin.

S-(+)-clopidogrel is commercially available in the name of Plavix™. This product is provided in a tablet form containing about 98 mg of S-(+)-clopidogrel hydrogen sulfate, which is equivalent to about 75 mg of S-(+)-clopidogrel base as active ingredients.

[Background Art]

General processes for the preparation of clopidogrel disclosed in U.S. patent Nos. 4,529,596, 4,847,265 and 5,204,469 are summarized in the following Scheme 1.
According to the processes of the conventional methods disclosed in the above Scheme 1, there is required a continuous optical resolution process of forming a diastereomeric salt (h) by reacting a clopidogrel racemate (g) with an optically active acid, obtaining a pure diastereomeric salt (h) of a dextrorotary (R)-optical isomer by recrystallization, and subsequently removing the optically active acid to prepare the S- (+)-clopidogrel as an optically pure dextrorotary isomer.
U.S. patent No. 4,847,265 discloses an optical resolution method for preparing S-(+)-clopidogrel using a (lR)-(−)-camphosulfonic acid as an optically active acid. WO 98/51689 discloses a process for preparing S-(+)-clopidogrel by conducting optical resolution and subsequent reactions from a compound of (e), wherein R is nitrile, carboxyamide or carboxylic acid.

Moreover, WO 02/059128 discloses a process for preparing S-(+)-clopidogrel by conducting optical resolution and subsequent reactions from a compound of Formula (g), wherein R is nitrile, carboxyamide or carboxylic acid.

As described above, the known processes of preparing S-(+)-clopidogrel may involve the optical resolution inevitably in a specific step of the continuous preparation processes. However, the optical resolution of clopidogrel racemates and an intermediate thereof is very disadvantageous environmentally and economically because it is unavoidable that all the levorotatory isomer and its intermediate are to be wasted, which could be at least 50% of the total amount of racemates. Moreover, the optical resolution process normally requires repetition of purification process such as recrystallization several times, thus causing the decrease in the yield.

WO 98/51689 discloses a method to overcome the above drawbacks, which is summarized in the following Scheme 2.
[Scheme 2]

In the convention process of Scheme 2, 2-(2-thienyl)-ethylamine of Formula (a) is reacted with o-chlorobenzaldehyde of Formula (j) and sodium cyanide. Thus obtained nitrile compound of Formula (k) is converted into an amide compound corresponding to a compound of Formula (l), and further converted to a methyl ester compound of Formula (m). An intermediate (m), an appropriate form used for synthesizing clopidogrel, may be prepared by reacting with an optically active acid via optical separation of amide (l) or ester (m). Finally, the optical isomer of Formula (m) is subjected to cyclization with formaldehyde in an acidic medium, thereby preparing clopidogrel.

European patent No. 466569 discloses another conventional process as summarized in the following Scheme 3:
wherein X is a halogen or a sulfonate group.

In the conventional process of Scheme 3, methyl 2-amino-(2-chlorophenyl)acetate of Formula (n) is reacted with 2-(2-thienyl)ethanol derivative of Formula (o), to provide an intermediate of Formula (m) (process A). Alternatively, methyl 2-halo-(2-chlorophenyl)acetate of Formula (p) is reacted with 2-(2-thienyl)ethylamine of Formula (a) to provide an intermediate of Formula (m) (process B).

Further, WO 99/18110 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 shown in 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) has a drawback that the compound is
difficult to purify by crystallization due to its relatively low melting point and high
solubility in an organic solvent.

As described above, there the conventional processes for preparing
clopidogrel are known to have many drawbacks.

[Disclosure]

[Technical Solution]

An object of the present invention is to provide an efficient process for
preparing S-(+)-clopidogrel with high optical and chemical purity in a simple
manner that a diastereomer salt is formed from a racemic carboxylic acid of
clopidogrel by using (+)-cinchonine through optical resolution followed by
extraction with an appropriate solvent.

An other object of the present invention is to provide a process for the
commercial mass production of S-(+)-clopidogrel by carrying out recycling of the
racemic carboxylic acid of clopidogrel, which is recovered by racemizing the filtrate
after separation of the diastereomer salt in a basic solution, at the same time along
with the process for preparing S-(+)-clopidogrel.
[Mode for Invention]

As shown in Scheme 5, the present invention relates to a process comprising: (i) preparing a diastereomer salt of Formula 4 as solid precipitates by reacting a racemic carboxylic acid of clopidogrel of Formula 2a and (+)-cinchonine of Formula 3 followed by a solid-liquid phase separation; (ii) preparing a carboxylic acid of S-(+)-clopidogrel of Formula 2b by desalting the diastereomer salt of Formula 4 under an acidic condition; and (iii) preparing S-(+)-clopidogrel of Formula 1 by reacting a carboxylic acid of S-(+)-clopidogrel of Formula 2b with methanol under an acidic condition; wherein a filtrate obtained after the phase separation of diastereomer salt in step i) is recycled after being converted to a racemic carboxylic acid of clopidogrel of Formula 2a by conducting sequential processes of desalting under an acidic condition and racemization under a basic condition.
Hereunder is provided a detailed description of each step of a process herein.

In step i), a racemic carboxylic acid of clopidogrel of Formula 2a is reacted with (+)-cinchonine of Formula 3, thus providing a diastereomer salt of Formula 4.

As a starting material in the present invention, the racemic carboxylic acid of clopidogrel of Formula 2a is easily obtained by the hydrolysis of racemic clopidogrel. Further, the (+)-cinchonine of Formula 3 has a chemical purity of 85% or higher and comprises less than about 15% of dihydrocinchonine.

The (+)-cinchonine of Formula 3 may be used in the amount of 0.5-1.0 equivalent relative to the racemic carboxylic acid of clopidogrel of Formula 2a. The ratio of carboxylic acid isomer of (R)-clopidogrel contained in the mother liquor to a cinchonine in the diastereomeric salt may vary depending on the equivalent ratio of (+)-cinchonine used. Ordinary solvent such as water, ketones, alcohols, ethers,
amides, esters, hydrocarbons, chlorohydrocarbons, nitriles and a mixture thereof may be used as a solvent. Preferable examples of the solvent are ketones, alcohols, nitriles or a mixture thereof.

The optical resolution is conducted by the formation of diastereomer salt using (+)-cinchonine as an optical resolving agent. Specifically, the optical resolution is conducted by means of a process of stirring or shaking and a process of standing of reactants using an organic solvent after the reaction with (+)-cinchonine. The optical resolution may be conducted at a temperature of between -30 °C and 60 °C, preferably at between -10 °C and 40 °C.

In step ii), a carboxylic acid of S-(+)/-clopidogrel of Formula 2b is prepared by using the diastereomer salt of Formula 4.

The diastereomer salt of Formula 4 is dissolved in water, desalted by the addition of an acid to be adjusted to pH 3-5, and extracted with an ordinary organic solvent, thus providing carboxylic acid of S-(+)/-clopidogrel of Formula 2b.

Inorganic acids such as hydrochloric acid, sulfuric acid and nitric acid and organic acids such as acetic acid may be used as the acid. Any solvent selected among ketones, alcohols, ethers, amides, esters, hydrocarbons, chlorohydrocarbons, nitriles and a mixture thereof may be used as an organic solvent. Preferable examples of the solvents are acetone, acetonitrile, methanol, ethanol, isopropanol, n-
butanol, f-butanol, ethylacetate, dichloromethane, toluene, diethylether, n-hexane and a mixture thereof.

The carboxylic acid of S-(+)-clopidogrel of Formula 2b, which is obtained by the extraction using the organic solvent, may be highly purified easily by means of an ordinary filtration. Optionally, the optical purity may further increased by controlling the solvent condition, preferably by means of recrystallization using organic solvent comprising acetone or acetonitrile.

In step iii), S-(+)-clopidogrel of Formula 1 is prepared by reacting the carboxylic acid of S-(+)-clopidogrel of Formula 2b under an acidic condition methanol.

The carboxylic acid of S-(+)-clopidogrel of Formula 2b is reacted with methanol under an acidic condition, where organic acid such as thionyl chloride is used in the amount of 1.0-2.0 equivalents, at a temperature of 40-80 °C, preferably at a reflux temperature, thus providing the desired S-(+)-clopidogrel of Formula 1.

Further, another feature of the present invention lies in the maximization of the yield of S-(+)-clopidogrel by preparing and recycling a racemic carboxylic acid of clopidogrel of Formula 2a by using a filtrate, which remains after collecting the diastereomer salt of Formula 4 as solid precipitates.

The diastereomer salt of Formula 4 is separated and collected as solid precipitates by means of a solid-liquid phase separation method. (R)-isomer is
enriched in the remaining filtrate. The present invention aims to improve the commercial utilization by collecting (R)-isomers as racemates and recycling them as a starting material.

Specifically, the diastereomer salt is desalted by adding an acid in the filtrate to be adjusted to pH 3-5. The racemic carboxylic acid of clopidogrel of Formula 2a is prepared and collected by conducting racemization of the diastereomer under a basic condition. The obtained racemic carboxylic acid of clopidogrel of Formula 2a is reused in step i).

As described in step ii), the acidic work-up of filtrate is an ordinary acid treatment, followed by extraction using an appropriate solvent. This acid treatment desalts the diastereomer salt and provides two isomers, i.e., a mixture of carboxylic acid intermediate of clopidogrel of Formulas 2c and 2b. A most portion of this mixture is (R)-isomer, and a small amount of (S)-isomer exists in this mixture.

The racemization of the obtained racemates is conducted under a basic condition of pH 9 or higher. Organic bases such as amines or inorganic bases such as alkali metal or alkaline earth metal may be used as a base. Preferable examples of the base are basic aqueous solution of sodium hydroxide or potassium hydroxide.

The racemization may be conducted by using a base in the amount of 1-20 equivalents relative to carboxylic acid of clopidogrel at a temperature of 30-150 °C, preferably at a reflux temperature. The degree of the racemization is measured by
using HPLC. The reaction is terminated when optical purity decreases below 10% e.e.

Reaction mixtures are neutralized and extracted according to the conventional method, and crystallized into solids by using a solvent such as ethyl ether, hexane, ethyl acetate, dichloromethane, acetonitrile and a mixture thereof.

Despite the aforementioned description, the steps i), ii) and iii) may be conducted continuously without being interrupted by the process of removing intermediates.

Further, S-(+) -clopidogrel of Formula 1 obtained according to the present invention may be manufactured into a pharmaceutically acceptable salt with an acid. Examples of the acid are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, fumaric acid, lactic acid, maleic acid, succinic acid and tartaric acid. S-(+) -clopidogrel of Formula 1 may also be reacted with alkali metal ion such as sodium or potassium ion or ammonium ion, thereby providing a pharmaceutically acceptable salt.

The present invention is described more specifically by the following Examples. Examples herein are meant only to illustrate the present invention, but they should not be construed as limiting the scope of the claimed invention.
**Example 1:** Preparation of diastereomer salt (4) using racemic carboxylic acid of clopidogrel (2a)

3.078 g (10 mmol) of racemic carboxylic acid of clopidogrel (2a) and 3.47 g (10 mmol) of 85% (+)-cinchonine were placed in a 250 mL flask, and completely dissolved in 100 mL of mixture of ethanol : acetonitrile (1:2, v/v). After stirring at room temperature for 18 hours, the produced solid precipitates were filtered at a reduced pressure and dried under vacuum at room temperature, thereby providing 1.74 g of white solid diastereomer salt (4).

Theoretical yield 58%; optical purity 98.9% (HPLC); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.85(4 IH, /=4.5 Hz), 8.28(d, IH, /=8.1 Hz), 8.02(dd, IH, /=8.1 Hz, 1.2 Hz), 7.24-7.76(m, 8H), 6.74(4 IH, /=5.1 Hz), 6.01-6.13(m, IH), 5.58(4 IH, /=5.1 Hz), 5.14(4 IH, /=9.3 Hz), 5.09(s, IH), 4.64(s, IH), 3.56-3.73(m, 2H), 3.25-3.32(m, 2H), 2.66-2.90(m, 7H), 2.28-2.34(m, IH), 1.95-2.03(m, IH), 1.75(brs, IH), 1.50-1.58(m, 2H), 1.32-1.36(m, IH)

**Example 2:** Preparation of diastereomer salt (4) using racemic carboxylic acid of clopidogrel (2a)

3.078 g (10 mmol) of racemic carboxylic acid of clopidogrel (2a) and 1.735 g (5 mmol) of 85% (+)-cinchonine were placed in a 250 mL flask, and completely dissolved in 100 mL of mixture of ethanol : acetonitrile (1:2, v/v). After stirring at
room temperature for 18 hours, the produced solid precipitates were filtered at a reduced pressure and dried under vacuum at room temperature, thereby providing 2.42 g of diastereomer salt (4).

Theoretical yield 80%; optical purity: 99.8% (HPLC)

**Example 3:** Preparation of diastereomer salt (4) using racemic carboxylic acid of clopidogrel (2a)

3.078 g (10 mmol) of racemic carboxylic acid of clopidogrel (2a) and 3.47 g (10 mmol) of 85% (−)-cinchonine were placed in a 250 mL flask, and completely dissolved in 100 mL of mixture of ethanol : acetone (1:2). After stirring at room temperature for 18 hours, the produced solid precipitates were filtered at a reduced pressure and dried under vacuum at room temperature, thereby providing 2.54 g of diastereomer salt (4).

Theoretical yield 84%; optical purity: 99.8% (HPLC)

**Example 4:** Preparation of diastereomer salt (4) using racemic carboxylic acid of clopidogrel (2a)

3.078 g (10 mmol) of racemic carboxylic acid of clopidogrel (2a) and 1.735 g (5 mmol) of 85% (+)-cinchonine were placed in a 250 mL flask, and completely dissolved in 100 mL of mixture of isopropanol : acetone (1:4, v/v). After stirring at
room temperature for 18 hours, the produced solid precipitates were filtered at a reduced pressure and dried under vacuum at room temperature, thereby providing 2.32 g of diastereomer salt (4).

Theoretical yield 77%; optical purity: 99.2% (HPLC)

**Example 5: Preparation of carboxylic acid (2b) of S-(+)-clopidogrel using diastereomer salt (4)**

Water (30 mL) was added in 2.4 g (4 mmol) of diastereomer salt (4) prepared in Example 2, followed by a slow addition of c-HCl to adjust pH to 4. This solution was extracted with dichloromethane (60 mL x 3 times), and the organic layer was dried with Na₂SO₄, filtered and concentrated, thereby providing 1.12 g of carboxylic acid (2b) of S-(+)-clopidogrel.

Yield 91%; optical purity: 99.0% (HPLC); ¹H NMR (300 MHz, CDCl₃) δ 9.16 (brs, IH), 7.96-7.99 (m, IH), 7.38-7.43 (m, IH), 7.25-7.30 (m, 2H), 7.16 (d, IH, /=5.1 Hz), 6.66 (d, IH, /=5.1 Hz), 5.24 (s, IH), 4.17-4.31 (m, 2H), 3.52-3.57 (m, IH), 3.30-3.32 (m, IH), 3.04 (brs, 2H)

**Example 6: Preparation of racemic carboxylic acid (2a) of clopidogrel using filtrate via racemization**

White solid diastereomer salt (4) prepared in Example 2 was separated, and the
filtrate was concentrated and added with water (20 mL), followed by a slow addition of c-HCl, thereby adjusting pH to 4. This solution was extracted with dichloromethane (30 mL x 3 times), and the organic layer was dried with Na$_2$SO$_4$, filtered and concentrated, thereby providing 1.8 g (optical purity 67% (HPLC), R-isomer dominant) of racemates comprising carboxylic acid of S-clopidogrel(2b) and carboxylic acid of R-clopidogrel(2c). Thus obtained racemates (1.8 g) was placed in a 50 mL flask, and added with a 20 mL aqueous solution of 10 N potassium hydroxide, followed by stirring at 110 °C for 40 hours. The temperature of the solution was lowered down to 5 °C, and added with c-HCl, thereby adjusting pH to 4. This solution was extracted with dichloromethane (30 mL x 3 times), and the organic layer was dried with Na$_2$SO$_4$, filtered and concentrated, thereby providing carboxylic acid of racemic clopidogrel (1.71 g, yield 95%, optical purity 0.3% (HPLC)).

**Example 7: Preparation of S-(+)-clopidogrel (1) using carboxylic acid (2b) of S-(+)-clopidogrel**

1.1 g (3.6 mmol) of carboxylic acid (2b) of S-(+)-clopidogrel prepared in Example 5 was added with 20 mL of methanol and 0.32 mL of SOCb, respectively, followed by stirring at 70 °C for 6 hours. The temperature of this solution was lowered down to room temperature, and concentrated at a reduced pressure, followed by the
addition of 10% NaHC$_3$(aq) to adjust pH to 7. This solution was extracted with dichloromethane (20 mL x 2 times), and the organic layer was dried with Na$_2$SC>4, filtered and concentrated at a reduced pressure. Thus obtained oil layer was washed with dichloromethane, passed through a small amount of silica gel column, and washed with ethylacetate:n-hexane (1:6, v/v). This solution was dried under vacuum at room temperature, thus providing 1.01 g of light yellow oil, i.e. (S)-(+) -clopidogrel (1).

Yield 88%; optical purity 99.2%(HPLC); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.68-7.71 (m, IH), 7.39-7.43 (m, IH), 7.27-7.30 (m, 2H), 7.06 (d, IH, /=5.1 Hz), 6.67 (d, IH, /=5.1 Hz), 4.92 (s, IH), 3.73(s, 3H), 3.61-3.78 (m, 2H), 2.88 (brs, 4H).

Example 8: Preparation of (S)-(+) -clopidogrel (1) using racemic carboxylic acid of clopidogrel (2a) via continuous reaction

3.078 g (10 mmol) of racemic carboxylic acid of clopidogrel (2a) and 1.735 g (5 mmol) of 85% (+)-cinchonine were placed in a 250 mL flask, and completely dissolved in 120 mL of isopropanol:acetonitrile (1:2, v/v). After stirring at room temperature for 18 hours, the produced solid precipitates were filtered at a reduced pressure and dried under vacuum at room temperature, thereby providing 2.4 g of diastereomer salt (4).

Water (30 mL) was added to 2.4 g (4 mmol) of thus obtained diastereomer salt
(4), and followed by a slow addition of c-HCl to adjust pH to 4. This solution was extracted with dichloromethane (60 mL x 3 times), and the organic layer was dried with Na₂SO₄, filtered and concentrated.

Thus obtained concentrates comprising carboxylic acid (2b) of S-(+)-clopidogrel was dissolved in 20 mL of methanol, and added with 0.35 mL of SOCl₂ 0.35 mL, followed by stirring at 70 °C for 6 hours. The temperature of this solution was lowered down to room temperature, and concentrated at a reduced pressure, followed by the addition of 10% NaHCO₃ (aq) to adjust pH to 7. This solution was extracted with dichloromethane (20 mL x 2 times), and the organic layer was dried with Na₂SO₄, filtered and concentrated at a reduced pressure. The obtained oil layer was dissolved in dichloromethane, passed through a small amount of silica gel column, and washed with ethylacetate : n-hexane (1:6), followed by vacuum-drying at room temperature, thereby providing 0.97 g of light yellow oil, i.e., (S)-(+) -clopidogrel (1).

Total yield 60%; optical purity 99.3%(HPLC); ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.71 (m, IH), 7.39-7.43 (m, IH), 7.27-7.30 (m, 2H), 7.06 (d, IH, /=5.1 Hz), 6.67 (d, IH, /=5.1 Hz), 4.92 (s, IH), 3.61-3.78 (m, 5H), 2.88 (s, 4H).

Optical purity of the compounds prepared in Examples 1-6 was measured by a chiral HPLC under the following HPLC conditions:
- Column: Ultron ES-OVM (Ovomucoid), 150 x 4.6 mm, 5.0 mm
- Flow rate: 1 mL/ minute
- Wavelength: 220 nm
- Eluent: methanol/ dibasic sodium phosphate buffering solution (2 nM, pH 7.5) (5/95, v/v)

Sample was dissolved in 0.1 mg/mL of a mixture of methanol/ dibasic sodium phosphate buffering solution (2 nM, pH 7.5) (5/95, v/v), and 10 mL of the sample was injected.

Optical purity of the compounds prepared in Examples 7-8 was measured by a chiral HPLC under the following HPLC conditions:

- Column: Ultron ES-OVM (Ovomucoid), 150 x 4.6 mm, 5.0 mm
- Flow rate: 1 mL/ minute
- Wavelength: 220 nm
- Eluent: dibasic sodium phosphate buffering solution (20 nM, pH 7)/acetonitrile (80/20, v/v)

Sample was dissolved in 0.1 mg/mL of a dibasic sodium phosphate buffering solution (20 nM, pH 7)/acetonitrile (80/20, v/v).
[Industrial applicability]

According to a process herein, a racemic carboxylic acid of clopidogrel is converted to a diastereomer salt by using (+)-cinchonine and optically resolved by using an appropriate solvent, thereby providing S-(+)-clopidogrel with relatively high optical and chemical purity. Further, R-isomer, which is contained in a filtrate remaining after the purification of the diastereomer salt, is racemized under a basic condition and collected as an intermediate of racemic carboxylic acid for recycling as a starting material. Therefore, the process of the present invention is useful for the commercial mass production of S-(+)-clopidogrel.
[CLAIMS]

[Claim 1]

A process for preparing S-(+)-clopidogrel, which comprises:

i) preparing a diastereomer salt of Formula 4 as solid precipitates by reacting a racemic carboxylic acid of clopidogrel of Formula 2a and (+)-cinchonine of Formula 3 followed by a solid-liquid phase separation;

ii) preparing a carboxylic acid of S-(+)-clopidogrel of Formula 2b by desalting the diastereomer salt of Formula 4 under an acidic condition; and

iii) preparing S-(+)-clopidogrel of Formula 1 by reacting a carboxylic acid of S-(+)-clopidogrel of Formula 2b with methanol under an acidic condition;

wherein a filtrate obtained from the phase separation of diastereomer salt in step i) is recycled after being converted to a racemic carboxylic acid of clopidogrel of Formula 2a by conducting sequential processes of desalting under an acidic condition and racemization under a basic condition.
[Claim 2]

The process of claim 1, wherein the (+)-cinchonine of Formula 3 is used in the amount of 0.5-1.0 equivalent relative to the racemic carboxylic acid of clopidogrel of Formula 2a.

[Claim 3]

The process of claim 1, wherein the racemization of the filtrate is conducted under a basic condition of pH 9 or higher.

[Claim 4]

The process of claim 3, wherein sodium hydroxide or potassium hydroxide is used as a base in the racemization.

[Claim 5]

The process of claim 1, wherein the carboxylic acid of S-(+)-clopidogrel of
Formula 2b is optically resolved by using a solvent selected from the group consisting of water, ketones, alcohols, ethers, amides, esters, hydrocarbons, chlorohydrocarbons, nitriles and a mixture thereof.

[Claim 6]

The process of claim 5, wherein the solvent comprises acetone or acetonitrile.

[Claim 7]

The process of claim 5, wherein the optical resolution is conducted by means of a process of stirring or shaking and a process of standing of reactants.

[Claim 8]

The process according to any of claims 5-7, wherein the optical resolution is conducted at a temperature of between -30 °C and 60 °C.

[Claim 9]

The process of claim 1 or 5, wherein the carboxylic acid of S-(+)-clopidogrel of Formula 2b is recrystallized, whereby increasing optical purity.

[Claim 10]

The process of claim 9, wherein the recrystallization is conducted in a solvent comprising acetone or acetonitrile.

[Claim 11]

The process of claim 1, wherein steps of i), ii) and iii) are conducted continuously without being interrupted by the process of isolating any
intermediates.
A. CLASSIFICATION OF SUBJECT MATTER

C07D 495/04(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)

C07D 495/04, C07D 498/02, A61K 31/47

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(CAplus, REG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No</th>
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<tr>
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<td>US 2006/0074242 A1 (MANOJ MADHUKARRAO DESHPANDE) 6 April 2006 See the whole document</td>
<td>1-1 I</td>
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<tr>
<td>A</td>
<td>US 673741 I B2 (TEVA PHARMACEUTICAL INDUSTRIES LTD ) 18 May 2004 See the whole document</td>
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<td>A</td>
<td>US 2004/02601 10 A1 (SANOFI-SYNTHELABO INC ) 23 December 2004 See the whole document</td>
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End of documentation

Further documents are listed in the continuation of Box C

See patent family annex

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Date of the actual completion of the international search

28 SEPTEMBER 2007 (28 09 2007)

Date of mailing of the international search report

28 SEPTEMBER 2007 (28.09.2007)

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