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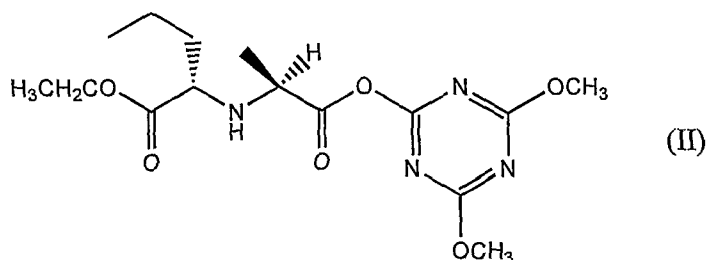
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(54) Title: PROCESS FOR THE PREPARATION OF N-[1-(S)-ETHOXYCARBONYL-1-BUTYL]-(S)-ALANINE-DMT COMPLEX AND ITS USE IN THE PREPARATION OF PERINDOPRIL



(57) Abstract: A compound N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex of Formula (II) is provided. Also provided is a process for the preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex and its use in preparing perindopril or a pharmaceutically acceptable salt thereof.

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PROCESS FOR THE PREPARATION OF N-[1-(S)-ETHOXYCARBONYL-1-BUTYL]-
(S)-ALANINE-DMT COMPLEX AND ITS USE IN THE PREPARATION OF
PERINDOPRIL

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to U.S. Provisional Application No. 60/792,875, filed on April 18, 2006, and entitled "PROCESS FOR THE PREPARATION OF N-[1-(S)-ETHOXYCARBONYL-1-BUTYL]-(S)-ALANINE-DMT COMPLEX AND ITS USE IN THE PREPARATION OF PERINDOPRIL" and Indian Provisional Application 125/MUM/2006, filed on January 25, 2006, entitled "PROCESS FOR THE PREPARATION OF N-[1-(S)-ETHOXYCARBONYL-1-BUTYL]-(S)-ALANINE-DMT COMPLEX AND ITS USE IN THE PREPARATION OF PERINDOPRIL", the contents of each of which are incorporated by reference herein.

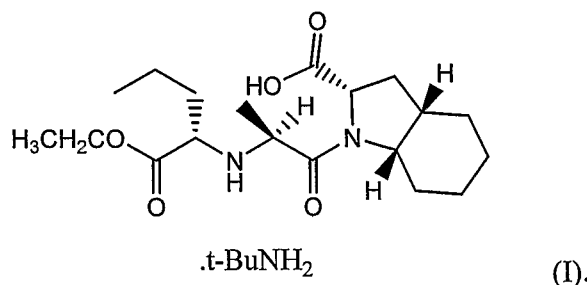
BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to a process for the preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex and its use for the preparation of perindopril.

2. Description of the Related Art

[0003] The present invention is directed to a process for the preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex and its use in the preparation of perindopril erbumine (also known as (2S,3aS,7aS)-1-[(S)-N-[(S)-1-carboxy-butyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1)) and represented by the structure of Formula I:

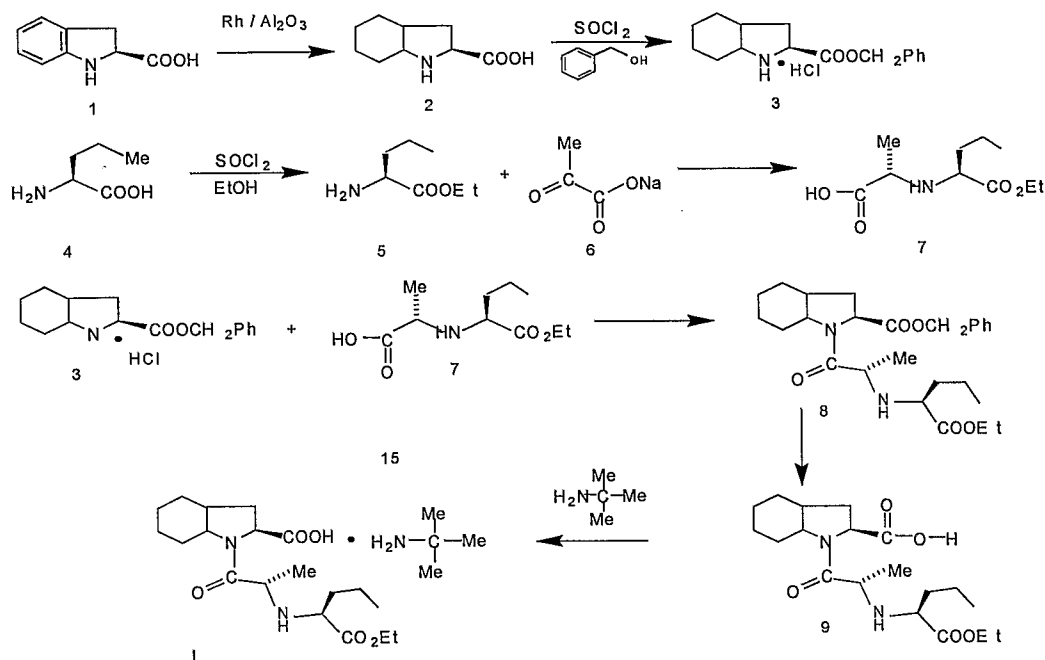


[0004] The tert-butylamine salt of perindopril, also known as perindopril erbumine, is the form commercially sold under the trade name Aceon[®]. Perindopril is the free acid form of perindopril erbumine and is an ethyl ester of a non-sulphydryl angiotensin-converting enzyme (ACE) inhibitor. Perindopril is a pro-drug and is metabolized in vivo by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite. Perindopril is ordinarily used to treat hypertension.

[0005] It is believed that perindoprilat lowers blood pressure primarily through inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes conversion of the inactive decapeptide, angiotensin I, to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

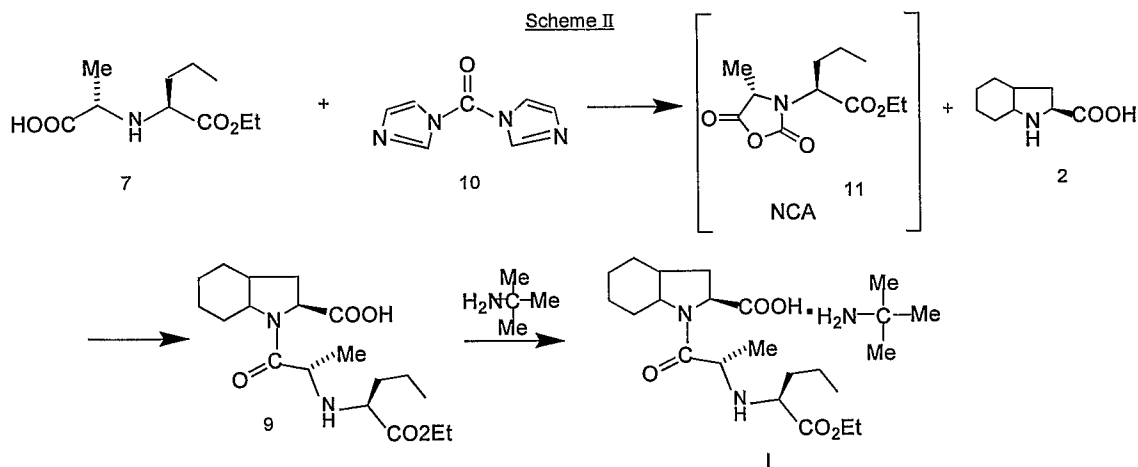
[0006] U.S. Patent No. 4,914,214 ("the '214 patent") discloses a process for the preparation of perindopril. In one process for the preparation of perindopril, indoline-2-carboxylic acid (1) is hydrogenated in methanol over a rhodium-aluminum oxide (Rh/Al₂O₃) catalyst to form (2S,3aS,7aS)-octahydroindole-2-carboxylic acid of the formula (2). The acid of formula (2) is esterified with thionyl chloride and benzyl alcohol to yield (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester (3), which is one of the key intermediates of perindopril. Another key intermediate of perindopril is prepared by reacting L-norvaline (4) with thionyl chloride and ethanol to form an ethyl ester (5). The ethyl ester (5) is reacted with sodium pyruvate (6) and subjected to hydrogenation to form N-1(S)-carboxyethylbutyl-(S)-alanine (7), another key intermediate. (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester (3) is then coupled with N-1(S)-carboxyethylbutyl-(S)-alanine (7) in the presence of sodium diethyldithiocarbamate trihydrate (DCC) to yield perindopril benzylated ester (8). Perindopril benzylated ester (8) is hydrolyzed to form perindopril (9). Perindopril (9) is reacted with tert-butylamine to form the perindopril erbumine salt (I) as shown in Scheme I:

Scheme 1



[0007] European Patent Application EP 1279665 also discloses a process for the preparation of perindopril. In this process, an N-carboxyanhydride (NCA) (11) is formed in-situ through the reaction of the intermediate N-1(S)-carboxyethyl butyl-(S)-alanine (7) with carbonyl diimidazole (10) as generally shown in Scheme II:

Scheme II

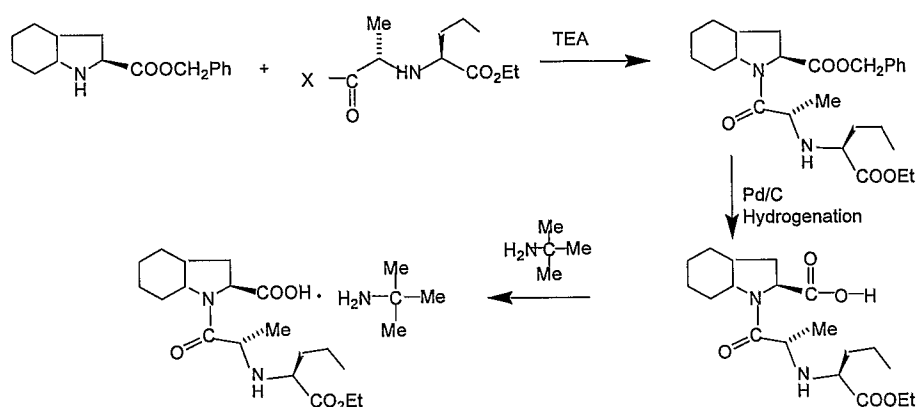


Next, N-carboxyanhydride (11) is reacted with (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (2) to yield perindopril (9). Again, the perindopril (9) is reacted with t-butylamine in ethyl acetate to form perindopril erbumine salt (I). However, the use of toxic and

hazardous phosgene for the preparation of the N-carboxyanhydride compound renders this method unsuitable for commercial manufacture.

[0008] WO 2004/075889 discloses a process for the preparation of perindopril comprising the reaction of the benzyl ester of (2S, 3aS, 7aS)-2-carboxyperhydroindole with N-[(S)-1-carbethoxybutyl]-(S)-alanyl chloride or bromide in the presence of a suitable base followed by debenzylation by catalytic hydrogenation as generally shown in Scheme III.

Scheme III

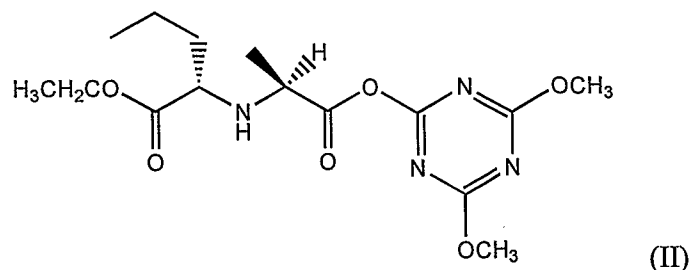


Due to hazardous chemicals and the preparation of an acid halide, this process is not environment friendly and cost effective.

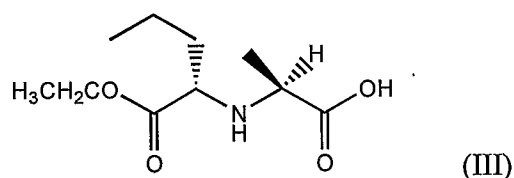
[0009] Kunishhima et al., Tetrahedron 57, pp. 1551-1558 (2001), Tetrahedron Letters, 40, pp. 5327-5330 (1999) and Tetrahedron Letters, 55, pp. 13159-13170 (1999) disclose the preparation of a 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) complex and then further coupling of various amino acids or normal acids with various substituted amines and alcohols to obtain amide and ester derivatives using the DMTMM complex.

SUMMARY OF THE INVENTION

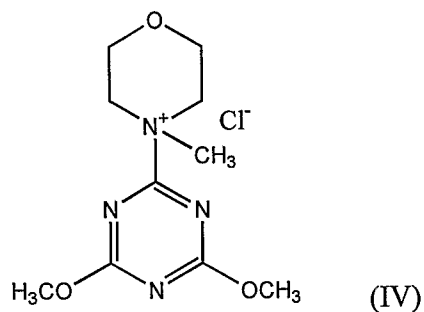
[0010] In one embodiment of the present invention, N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex of Formula II is provided:



[0011] In a second embodiment of the present invention, a process for the preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex is provided, the process comprising reacting N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine of Formula III:

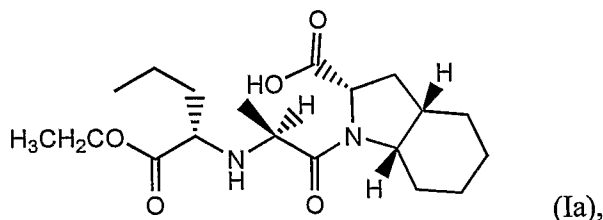


with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride ("DMTMM") of Formula IV:



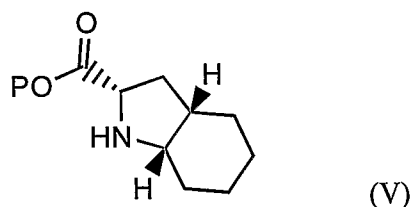
in a solvent to provide the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex.

[0012] In a third embodiment of the present invention, a process for the preparation of perindopril of Formula (Ia) is provided:

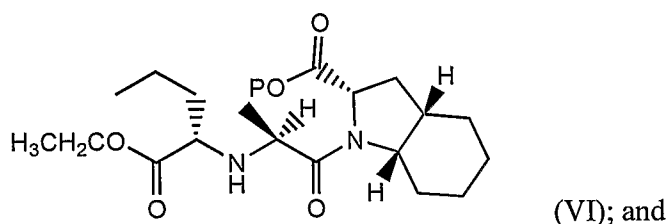


the process comprising:

(a) reacting N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex with a protected (2S, 3aS, 7aS)-2-carboxyperhydroindole compound of Formula V,



wherein P is a protection group which may be an aryl, alkyl, or silyl group, in a solvent to provide a compound of Formula VI:



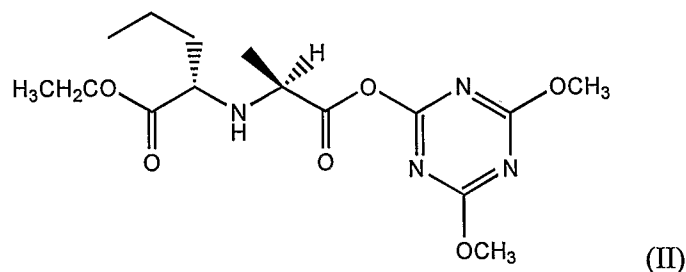
(b) deprotecting the compound of Formula VI using a suitable deprotecting agent to provide perindopril. In a further aspect of the present invention, this process may be followed by salt formation to provide perindopril erbumine.

[0013] The advantages of the present invention include at least:

1. The process does not require hazardous chemicals.
2. The process avoids low temperatures.
3. The process does not require the use of expensive reagents and catalysts.
4. The process provides relatively high yields with a relatively short process.
- (5) The process avoids tedious crystallization.

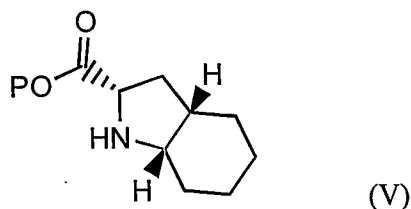
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] One aspect of the present invention is directed to N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex of Formula II

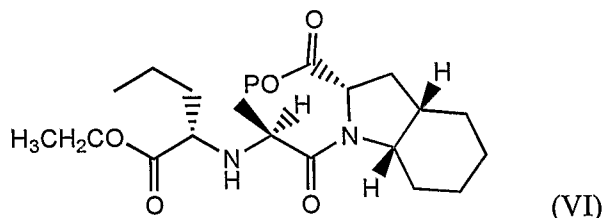


[0015] The N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex can be obtained by a process involving at least the reaction of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine with DMTMM in the presence of a solvent. Generally, this reaction may be carried out under atmospheric pressure. Suitable solvents for use in the reaction may be an organic solvent such as, for example, tetrahydrofuran, tert-butyl methyl ether, diisopropyl ether, ethyl acetate, isopropyl acetate, n-butyl acetate, n-hexane, a petroleum ether, n-heptane, acetonitrile, acetone, methyl isobutyl ketone, water and the like and mixtures thereof. Preferably the solvent is tetrahydrofuran. Generally, DMTMM may be present in the reaction in a molar proportion of about 1 to about 1.5 moles per mole of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine, and preferably about 1.0 to about 1.25 moles per mole of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine. The temperature of the reaction may range from about 20°C to about 80°C, and preferably from about 20°C to about 40°C.

[0016] In another aspect of the present invention, the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex of Formula II is thereafter converted to perindopril or a derivative thereof or a pharmaceutically acceptable salt thereof. In one embodiment, the process for the preparation of perindopril or a derivative thereof or a pharmaceutically acceptable salt thereof includes at least (a) reacting N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex with a (2S, 3aS, 7aS)-2-carboxyperhydroindole of Formula V:



wherein P is a protection group which may be an aryl, alkyl, or a silyl group, in a solvent to provide a compound of Formula VI:



(b) followed by deprotection of the compound of Formula VI using a suitable deprotecting agent to provide perindopril; and (c) optionally preparing a salt of perindopril. The (2S, 3aS, 7aS)-2-carboxyperhydroindole of Formula V is a known compound, which may be prepared in accordance with methods known in the art, for example, the methods disclosed in U.S. Patent Nos. 4,508,749; 4,935,525 and 5,258,525; U.S. Patent Application Publication No. 2005/0171165; and European Patent Nos. 0037231 and 0132580 all of which are incorporated by reference herein.

[0017] The reaction N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex with a (2S, 3aS, 7aS)-2-carboxyperhydroindole of Formula V may be carried out under atmospheric pressure. A suitable solvent for use in step (a) of the reaction may be an organic solvent such as, for example, tetrahydrofuran, tert-butyl methyl ether, diisopropyl ether, ethyl acetate, isopropyl acetate, n-butyl acetate, n-hexane, a petroleum ether, n-heptane, acetonitrile, acetone, methyl isobutyl ketone, water and the like and mixtures thereof, with tetrahydrofuran being preferred. The compound of Formula V may be present in a molar proportion of about 1 to about 1.5 moles per mole of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex, and preferably from about 1 to about 1.25 moles per mole of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex.

[0018] The temperature of step (a) of the reaction may range from about 20°C to about 110°C and preferably from about 20°C to about 50°C. The reaction time of step (a) of the reaction may vary from about 2 to about 24 hours, and preferably from about 5 to

about 12 hours. The reaction mass containing the compound of Formula VI may be quenched in, for example, a saturated sodium chloride solution, and then separating the phases, e.g., extracting the aqueous layer with an appropriate organic solvent such as dichloromethane, washed with water, or the organic solvent evaporated to obtain the compound of Formula VI, which may then be taken into the next deprotecting step.

[0019] In step (b) of the reaction, the compound of Formula VI is deprotected using a suitable deprotecting agent to provide perindopril. In one embodiment, the compound of Formula VI may be deprotected by catalytic hydrogenation using a suitable deprotection agent such as a group VIII transition metal catalyst, e.g., palladium, platinum, platinum dioxide, iridium, rhodium, ruthenium and titanium, with an appropriate support such as carbon, alumina, barium carbonate, barium sulfate, calcium carbonate, kieselguhr (diatomaceous earth), silica-alumina, silica-gel, strontium carbonate, tin oxide, titania, alumina powder and the like. The metal catalyst can be employed either in the inactivated form or activated form. Suitable forms in which the catalysts are employed include powder, granules, extrudate, pellets and spheres. The hydrogenation may take place in an organic or inorganic solvent or in admixture with water or a mixture thereof, such as alcohols, e.g., methanol and ethanol; aliphatic ketonic solvents, e.g., acetone, methyl ethyl ketone and methyl isobutyl ketone; cyclic ketones, e.g., cyclopentanone and cyclohexanone; ether solvents, e.g., tetrahydrofuran, diethyl ether, diisopropyl ether, glyme and diglyme; aliphatic hydrocarbons, e.g., n-pentane, n-hexane and n-heptane; cyclic hydrocarbons, e.g., cyclopentane and cyclohexane; and aromatic hydrocarbons e.g., benzene and toluene and the like. Preferably the solvent is an alcohol such as ethanol or an aromatic hydrocarbons such as toluene.

[0020] In another embodiment, when the compound of Formula VI is protected with a silyl protection group, the compound of Formula VI may be deprotected under acidic or neutral conditions in the presence of acidic or alcoholic catalysts. The acidic catalyst may be hydrochloric acid, acetic acid, trifluoroacetic acid, sulfuric acid, hydrobromic acid and the like and mixtures thereof. The alcoholic catalyst may be methanol, ethanol, butanol, propanol, isopropyl alcohol, benzyl alcohol and the like and mixtures thereof.

[0021] The temperature of step (b) may range from about 20°C to about 110°C, and preferably from about 20°C to about 50°C. The time of step (b) to complete deprotection of the compound of Formula VI may vary from about 2 to about 24 hours, and preferably about 5 to about 12 hours. At the end of the reaction, the catalyst may be filtered off and the solvent may be evaporated to provide perindopril base of Formula (Ia), which may then be crystallized from any of the aforesaid solvents or mixtures thereof.

[0022] Optionally, the perindopril base obtained in step (b) may be further reacted to prepare a salt of perindopril. The salt formation step is known in the art as demonstrated in the '214 patent. Preferably, the erbumine (tert-butyl) salt of perindopril is obtained by reacting perindopril with tert-butylamine as known in the art. The salt formation may be followed by crystallization from any of the aforesaid solvents or mixtures thereof.

[0023] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention.

EXAMPLE 1

[0024] Preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex

[0025] Into a round bottom flask, tetrahydrofuran (25 ml), N-1(S)-carboxyethylbutyl-(S)-alanine (1.0g) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (1.274 g) were added. The reaction mass was stirred for about 10 minutes at a temperature ranging from about 20°C to about 25°C under nitrogen. The resulting solution contained the complex of Formula II.

EXAMPLE 2

[0026] Preparation of benzyl ester of Perindopril

[0027] Benzyl (2S,3aS,7aS)-benzyl-perhydroindole-2-carboxylate (1.193 g) was added to the solution from Example 1 at a temperature ranging from about 20°C to about 25°C under nitrogen. The reaction mass was stirred for about 5 to about 6 hours. The reaction was monitored by TLC. After the reaction was completed as determined by TLC

(showing less than 5% of unreacted benzyl (2S,3aS,7aS)-benzyl-perhydroindole-2-carboxylate), the reaction mass was poured into a saturated aqueous sodium chloride solution. The reaction mixture was stirred for about 5 minutes and the layers were separated. The aqueous layer was extracted with dichloromethane and the combined layer was evaporated under reduced pressure at a temperature ranging from about 40°C to about 45°C to obtain perindopril benzyl ester (1.5 g).

EXAMPLE 3

[0028] Preparation of Perindopril tert-butyl amine salt

[0029] Perindopril benzyl ester (1.0 g) obtained in Example 2 was dissolved in absolute ethanol (10 ml) under nitrogen. The system was flushed with nitrogen for about 15 minutes and charged with 10% palladium on carbon (5% w/w) and hydrogenated by bubbling hydrogen gas after replacing nitrogen at room temperature until the completion of reaction. After completion of the reaction as determined by TLC (showing the substantial absence of perindopril benzyl ester), the reaction mass was concentrated under reduced pressure and dissolved in methylene chloride (20 ml).

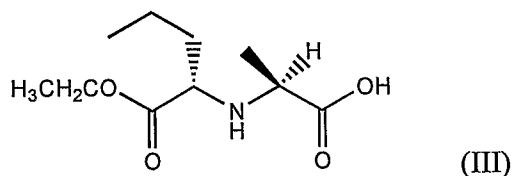
[0030] Next, the methylene chloride solution was charged in a round bottom flask and cooled to a temperature of about 10°C. Tert-butyl amine (0.5 ml) was charged in 30 minutes while maintaining the temperature below about 10°C and stirred further for about 30 minutes at a temperature ranging from about 35°C to about 40°C. Methylene chloride was then distilled off completely and a mixture of isopropyl alcohol (3 ml), acetone (6 ml) and acetonitrile (6 ml) was charged and heated to a temperature of about 65-70°C to get a clear solution. The reaction mass was cooled slowly to a temperature of about 25°C over about 2 hours and then further cooled to a temperature of about 5 to about 10°C and then filtered. The material was then dried under vacuum at a temperature of about 40°C. (Weight: 0.8 g, purity: >97% by HPLC).

[0031] Specific optical rotation $[\alpha]_D = -66$ (C=1%, Methanol), IR (KBr) spectrum shows the following absorptions (cm^{-1}) 3300, 2930, 1744, 1732m, 1644m, 1568. The ^1H -NMR (CDCl_3) shows the following signals at δ 4.28-4.12 (m, 1H), 4.18-4.09 (q, 2H), 3.76 (m, 2H), 3.53 (q, 1H), 3.1 (t, 1H), 2.32-2.14 (m, 2H), 2.01 (m, 1H), 1.75-1.62 (m, 4H), 1.32 (m, 2H), 1.30 (s, 9H), 1.28 (t, 3H), 0.88 (t, 3H). C.I. Mass shows m/z at 368 (base peak).

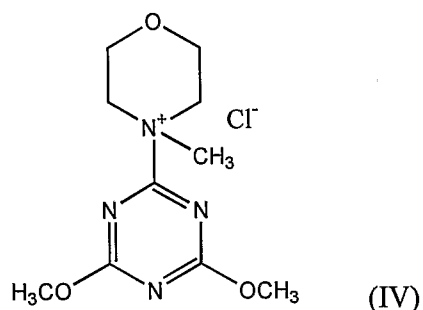
[0032] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

WHAT IS CLAIMED IS:

1. A process for the preparation of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex, the process comprising reacting N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine of formula III:



with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride ("DMTM") of Formula IV:



in a solvent to provide the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex.

2. The process of Claim 1, wherein the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex is thereafter converted to perindopril or a pharmaceutically acceptable salt thereof.

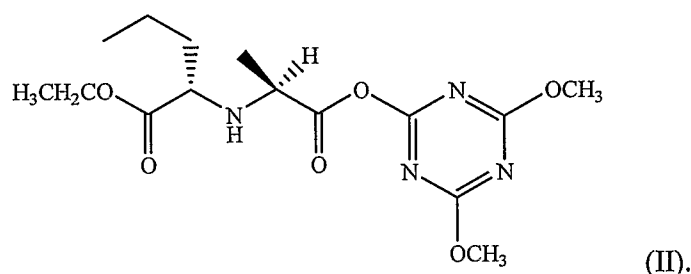
3. The process of Claim 1, wherein the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex is thereafter converted to perindopril erbumine.

4. The process of Claim 1, wherein the N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex is thereafter converted to an alpha polymorph of perindopril erbumine.

5. Perindopril erbumine prepared in accordance with the process of Claims 1-4 having a purity of greater than about 95%.

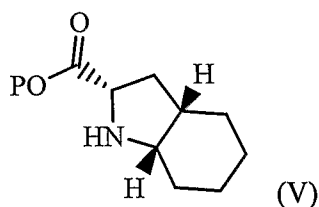
6. Alpha polymorph of perindopril erbumine prepared in accordance with the process of Claims 1-4 having a purity of greater than about 95%.

7. A compound of Formula II:

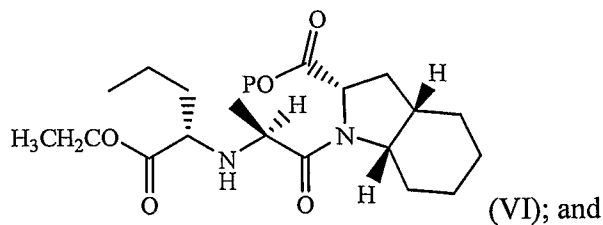


8. A process for the preparation of perindopril or a pharmaceutically acceptable salt thereof, the process comprising:

(a) the reaction of N-[1-(S)-ethoxycarbonyl-1-butyl]-(S)-alanine-DMT complex with a protected (2S, 3aS, 7aS)-2-carboxyperhydroindole of compound formula V,



wherein P is a protection group which may be an aryl, alkyl, or silyl group, in a solvent to provide a compound of Formula VI



(b) deprotecting the compound of Formula VI using a suitable deprotecting agent to provide perindopril.

9. The process of Claim 8, further comprising converting perindopril to a pharmaceutically acceptable salt thereof.

10. The process of Claim 8, further comprising converting perindopril to an alpha polymorph of perindopril erbumine.