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(54) **Title**: PROCESS FOR THE PREPARATION OF AN INTERMEDIATE OF CILAZAPRIL

(57) **Abstract**: The present invention relates to a process for the preparation of optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid, an intermediate for the preparation of cilazapril.

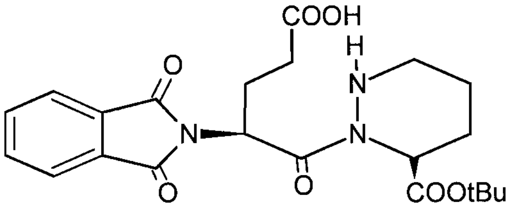
PROCESS FOR THE PREPARATION OF AN INTERMEDIATE OF CILAZAPRIL

Field of the Invention

The present invention relates to a process for the preparation of optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I, an intermediate for the preparation of cilazapril.

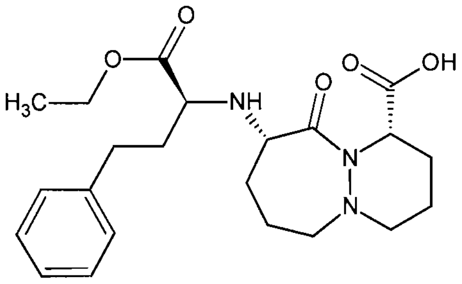
Background of the Invention

Optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I,



Formula I

is a useful intermediate for the preparation of cilazapril, an angiotensin converting enzyme (ACE) inhibitor. Cilazapril is chemically described as (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino [1,2-a][1,2]diazepine-1-carboxylic acid represented by Formula II.



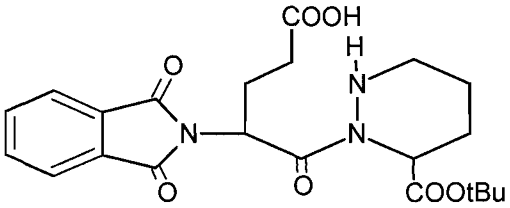
Formula II

Processes for the preparation of the compound of Formula I are described in U.S. Patent Nos. 4,512,924 and 6,201,118; PCT Publication Nos. WO 01/56997; WO 99/55724; WO 2005/122682; and Canadian Patent No. 2,500,558.

U.S. Patent No. 4,512,924 describes a process for the preparation of (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of

Formula I having a specific optical rotation of -54.4° by crystallization from ethyl acetate and diethyl ether.

Canadian Patent No. 2,500,558 describes the use of mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA;



Formula IA

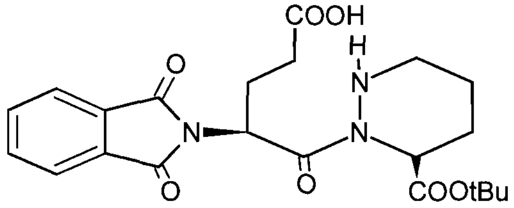
for the preparation of cilazapril and involves enantiomeric separation in the later stage.

Summary of the Invention

Reported processes for the preparation of (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I are commercially unviable in one or more ways. They involve the use of low boiling, costly and highly inflammable solvents, use column chromatography at industrial scale, or enantiomeric separation at later, value-added stages, leading to unacceptable losses. Thus there is a need for a commercially viable process that can be easily used at commercial scale. The present inventors have developed such a process, which involves the preparation of optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I, which is further converted to cilazapril. In the process of the present invention, instead of the four diastereomers (RR, SS, RS and SR), which are obtained and separated in the reported processes, only two diastereomers (SS and SR) are formed and only the SS diastereomer is carried forward though the purification of the uncyclized acid intermediate (compound of Formula I). This process avoids additional steps, such as column chromatography, and does not involve enantiomeric separation in the final stage and it provides significant cost and productivity advantages.

Detailed Description of the Invention

An aspect of the present invention provides a process for the preparation of optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I,



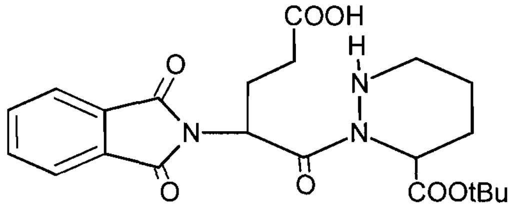
Formula I

wherein, the process comprises:

a) treating a mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA with an ester solvent and an aliphatic hydrocarbon solvent; and

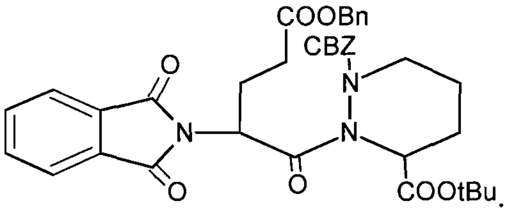
b) isolating optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I from the reaction mixture thereof.

The mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA



Formula IA

is prepared by the hydrogenation of 6-t-butoxycarbonyl-hexahydro-1-pyridazinyl-(N^1-benzyloxycarbonyl)-carbonyl-1,3-dioxo-2-isoindolebutyric acid benzyl ester of Formula IB



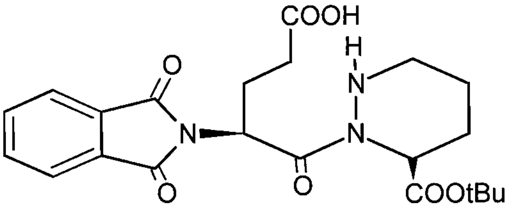
Formula IB

in the presence of a solvent, such as methanol, tetrahydrofuran or dichloromethane and a catalyst such as palladium/carbon.

6-t-Butoxycarbonyl-hexahydro-1-pyridazinyl-(N^1-benzyloxycarbonyl)-carbonyl-1,3-dioxo-2-isoindolebutyric acid benzyl ester of Formula IB as a racemic mixture known in the art may be used for preparing a mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA. The mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA may be first treated with an ester solvent followed by treatment with a mixture of an ester solvent and an aliphatic hydrocarbon solvent. Examples of the ester solvent are ethyl acetate, methyl acetate, t-butyl acetate, for example, ethyl acetate or a mixture thereof. Examples of the aliphatic hydrocarbon solvent are hexanes, n-pentane, heptane or a mixture thereof.

The ratio of the ester solvent to the aliphatic hydrocarbon solvent for treatment with compound of Formula IA may vary, from about 1.5:1.0 to about 5.0:1.0. The ratio is preferably from about 2.0:1.0 to about 3.0:1.0. The treatment with the ester solvent and the aliphatic hydrocarbon solvent may be carried out at a temperature of about 10°C to about 70°C, preferably at about 25°C to about 40°C. The treatment with ester solvent and aliphatic hydrocarbon solvent may be carried for about 10 minutes to about 5 hours, preferably for about 30 minutes to about 3 hours. The optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I may be isolated by filtration, decantation, or a combination thereof.

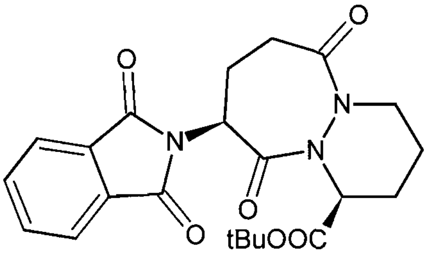
(S,S)-6-t-Butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I



Formula I

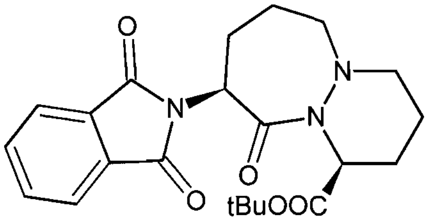
may be further converted to cilazapril of Formula II using the processes described in PCT Publication Nos. WO 2004/078761 and WO 2005/122682; Canadian Patent No. 2,500,558; and U.S. Patent No. 4,512,924.

6-t-Butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I is cyclized in the presence of a solvent, for example dichloromethane, to obtain 6-t-butyl octahydro-6,10-dioxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)-carboxylate of Formula III.



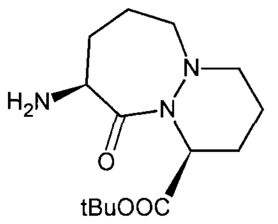
Formula III

6-t-butyl octahydro-6,10-dioxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)-carboxylate of Formula III is reduced in the presence of a solvent, for example Tetrahydrofuran, and a Lewis acid, such as borane, to obtain 6-t-butyl octahydro-10-oxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)-carboxylate of Formula IV.



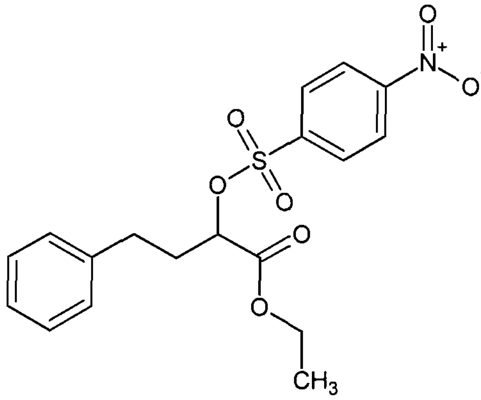
Formula IV

6-t-Butyl octahydro-10-oxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)-carboxylate of Formula IV is hydrolyzed to obtain 9-amino-octahydro-10-oxo-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylic acid t-butyl ester of Formula V.



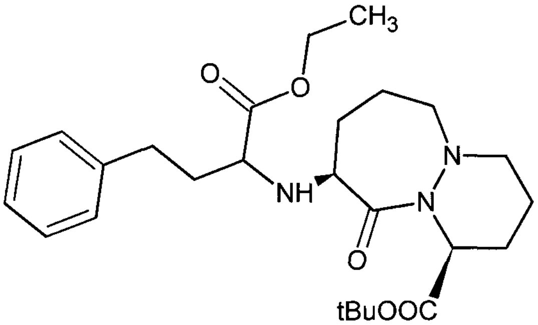
Formula V

9-Amino-octahydro-10-oxo-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylic acid t-butyl ester of Formula V is reacted with Ethyl (+)-R-2-4-nitrobenzene-sulfonyloxy-4-phenyl-butyrate of Formula VI



Formula VI

in the presence of a base, for example N-methylmorpholine, to obtain t-butyl (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate of Formula VII.



Formula VII

t-Butyl (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate of Formula VII is deprotected and optionally further purified to obtain (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid, cilazapril of Formula II.

In the following section, embodiments are described by way of examples to illustrate the process of invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

EXAMPLES

Example 1: Preparation of (S,S)-6-t-Butoxycarbonyl-Hexahydro-1-Pyridazinylcarbonyl-1,3-Dioxo-2-Isoindolebutyric Acid

Step 1) Preparation of 6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid

6-t-Butoxycarbonyl-hexahydro-1-pyridazinyl-(N-benzyloxycarbonyl)-carbonyl-1,3-dioxo-2-isoindolebutyric acid benzyl ester (300 g) was added to methanol (900 mL) and the solution was stirred at 25°C to 30°C to make clear solution. Activated carbon (15 g) was added to the above solution at 25°C to 30°C. The solution was stirred for 25 minutes and filtered. 10% palladium/carbon (60 g, 50% wet) and deionized water (75 mL) were added to the filtrate in an autoclave at 25°C to 30°C. The reaction mixture was hydrogenated at a pressure of 7.0 to 7.5 kg/cm^2 at 30°C to 35°C for 3 hours. The reaction mixture was filtered and washed with methanol (600 mL). Methanol was recovered completely from the reaction mixture under vacuum to obtain the title compound.

Step 2) Preparation of (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinyl carbonyl-1,3-dioxo-2-isoindolebutyric acid

6-t-Butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dihydro-1,3-dioxo-2-isoindoline butyric acid (170 g) (specific optical rotation $[\alpha]_D^{25}$ 1% Methanol: -27.3°) was added to ethyl acetate (340 mL) at 20°C to 30°C and stirred for 15 minutes. Ethyl acetate was recovered completely under vacuum. A mixture of ethyl acetate (340 mL) and hexanes (170 mL) at 25°C to 30°C was added to the residue and stirred for 2 hours at 25°C to 30°C. The solid obtained was filtered and washed with a mixture of ethyl acetate (85 mL) and hexanes (85 mL). The product obtained was dried in an air oven at 35°C to 40°C until moisture content was less than 3% to obtain the title compound (48 g).

Chromatographic Purity: 93.04%

Specific Optical Rotation $[\alpha]_D^{25}$ 1% Methanol: -51.8°

Example 2: Preparation of Cilazapril

Step 1) Preparation of 6-t-butyl octahydro-6,10-dioxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylate:

(S,S)-6-t-Butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid (300 g) was added to dichloromethane (2400 mL) and stirred for 10 minutes to make a clear solution at 25°C to 30°C under nitrogen. The reaction mixture was cooled to 10°C to 15°C. A mixture of thionyl chloride (104.3 g) and dichloromethane (300 mL) was slowly added to the reaction mixture in 60 minutes at 10°C to 15°C under nitrogen. The reaction mixture was stirred for 2 hours. The reaction mixture was added to a solution of sodium bicarbonate (300 g in 3000 mL deionized water) at 0°C to 5°C. The temperature was increased to 25°C to 30°C and 10% sodium chloride solution (1500 mL) was added to the reaction mixture. The solution was stirred for 15 minutes and the layers obtained were separated. The aqueous layer was extracted with dichloromethane (600 mL). The two organic layers were combined and dichloromethane was recovered completely under vacuum to obtain the title compound (246 g).

Step 2) Preparation of 6-t-butyl octahydro-10-oxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylate:

6-t-Butyl octahydro-6,10-dioxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]-diazepine-1-(S)carboxylate (240 g) was added to tetrahydrofuran (1200 mL) at 25°C to 30°C under nitrogen. The reaction mixture was stirred for 10 minutes and cooled to 0°C to 5°C under nitrogen. Borane-tetrahydrofuran complex (720 mL) was added to the reaction mixture in 60 minutes at 0°C to 5°C under nitrogen and stirred for 2 hours at 0°C to 5°C. Dichloromethane (2400 mL) was added to the reaction mixture at 0°C to 5°C. The temperature of the reaction mass was increased to 5°C to 10°C and hydrochloride solution (1200 mL) was slowly added. The reaction mixture was stirred and the layers obtained were separated. The aqueous layer was extracted with dichloromethane (240 mL). The two organic layers were combined and washed with 5% sodium bicarbonate

(2400 mL). The solvents were recovered completely from organic layer under vacuum. A mixture of denatured spirit (180 mL) and deionized water (72 mL) was added to the reaction mixture and stirred for 30 minutes. Deionized water (84 mL) was added to the reaction mixture, stirred for 30 minutes and the solid obtained was filtered. The solid obtained was washed with a mixture of denatured spirit (60 mL) and deionized water (180 mL). The product was dried in an air oven at 35°C to 40°C until moisture content was less than 5% (192 g) to obtain the title compound.

Chromatographic Purity: 97.45%

Step 3) Preparation of 9-amino-octahydro-10-oxo-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylic acid t-butyl ester:

6-t-Butyl octahydro-10-oxo-9-(S)-phthalimido-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylate (170 g) was dissolved in denatured spirit (1700 mL) and hydrazine hydrate (51 g) was added at 25°C to 30°C under nitrogen. The reaction mixture was stirred at 25°C to 30°C for 2 hours to 6 hours. Denatured spirit was recovered completely under vacuum and 2N acetic acid (1700 mL) was added. The reaction mixture was stirred for 5 hours, filtered and washed with deionized water (850 mL). The pH of the filtrate was adjusted to 7.9 to 8.0 with 2N sodium hydroxide (1690 mL), and dichloromethane (850 mL) was added. The reaction mixture was stirred for 15 minutes and the layers obtained were separated. The aqueous layer was extracted with dichloromethane (850 mL). The two layers were combined and dried over anhydrous sodium sulphate (34 g). Dichloromethane was recovered completely under vacuum to get the title compound (110 g) which is used as such *in situ* for the next step.

Step 4) Preparation of t-butyl (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate:

Toluene (550 mL), ethyl (+)-R-2-(4-nitrobenzene-sulfonyloxy)-4-phenyl butyrate (168 g) and N-methyl morphline (47 g) were added to 9-amino-octahydro-10-oxo-6H-pyridazo[1,2a][1,2]diazepine-1-(S)carboxylic acid t-butyl ester, obtained above, at 25°C to 30°C. The temperature was increased to 75°C and stirred at 75°C to 80°C. The reaction mixture was cooled to 25°C to 30°C and deionized water (330 mL) was added. The pH was adjusted to 8.5 to 8.8 with 2N aqueous sodium carbonate solution (350 mL). The reaction mixture was stirred for 15 minutes, the layers were separated and the organic layer was washed with deionized water (330 mL). Toluene was recovered completely under vacuum to get the title compound (205 g) which is used as such *in situ* for the next step.

Step 5) Preparation of crude (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid:

Dichloromethane (550 mL) was added to t-butyl(1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate at 25°C to 30°C. The reaction mixture was cooled to -5°C and anhydrous HCl gas was added at -5°C to 0°C for 7 hours. Dichloromethane was recovered completely under vacuum. Diethyl ether (550 mL) and deionized water (550 mL) were added to the reaction mixture, stirred for 15 minutes and the layers obtained were separated. The aqueous layer was extracted with diethyl ether. The two organic layers were combined and washed with 1N hydrochloride solution (363 mL). The two aqueous layers were combined and the pH was adjusted to 4.4 to 4.5 with 10% sodium hydroxide solution (350 mL) at 25°C to 30°C.

Dichloromethane (550 mL) was added to the reaction mixture and stirred for 15 minutes, the layers were separated and aqueous layer was extracted with dichloromethane (220 mL). Dichloromethane was recovered under vacuum. Denatured spirit (550 mL) was added to the reaction mixture, temperature was raised to 40°C and stirred at 35°C to 40°C. Activated carbon (11 g) was added at 35°C to 40°C and stirred for 30 minutes at 35°C to 40°C. The reaction mixture was filtered and washed with denatured spirit (220 mL) at 25°C to 30°C. Denatured spirit (660 mL) was recovered under vacuum and deionized water (230 mL) was added slowly in 1 hour to 2 hours at 40°C to 45°C. The reaction mixture was stirred for 2 hours at 40°C to 45°C and cooled to 30°C to 35°C. The reaction mixture was stirred for 2 hours at 30°C to 35°C and the solid obtained was filtered. The solid obtained was washed with a mixture of denatured spirit (44 mL), deionized water (176 mL) and hexanes (110 mL) at 25°C to 30°C. The solid obtained was washed with diethyl ether (220 mL) and dried under vacuum at 30°C to 35°C until the moisture content was less than 8% to obtain the title compound (74 g).

Step 6) Purification of crude (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid:

Denatured spirit (325 mL) was added to (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (65 g) at 25°C to 30°C. The temperature was increased to 40°C and stirred at 35°C to 40°C. Activated carbon (3.6 g) was added at 30°C to 40°C. The reaction mixture was stirred for 30 minutes, filtered and washed with denatured spirit (130 mL). Denatured spirit (390 mL) was recovered under vacuum and deionized water (140 mL) was added slowly in 1 hour to 2 hours at 40°C to 45°C. The reaction mixture was cooled to 35°C, stirred for 2 hours and filtered at 30°C to 35°C. The solid obtained was washed with a mixture of previously chilled denatured spirit (26 mL) and deionized water (104 mL) at 5°C to 8°C. The solid obtained was dried under vacuum at 30°C to 35°C until the water content was 3.5% to 4.5% to obtain the title compound.

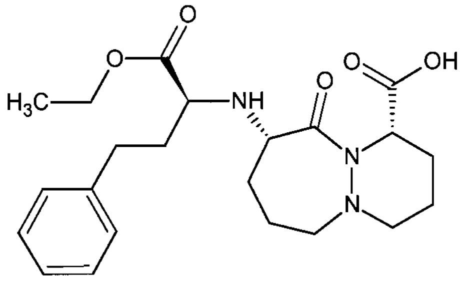
Yield: 52 g

Chromatographic purity: 99.90%

Specific optical rotation $[\alpha]_D^{25}$ 1% Methanol: -395.0°

We claim

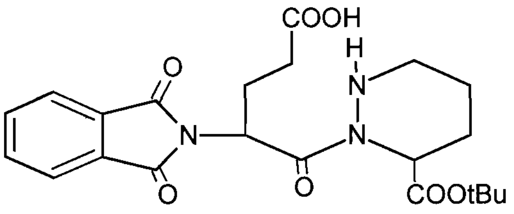
1. A process for the preparation of optically pure (1S,9S)-9-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-10-oxooctahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid of Formula II



Formula II

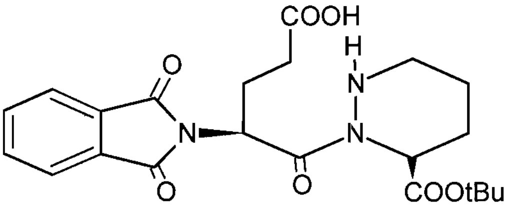
wherein the process comprises:

a) treating a mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula IA with an ester solvent and an aliphatic hydrocarbon solvent, and;



Formula IA

b) isolating optically pure (S,S)-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid of Formula I from the reaction mixture thereof.



Formula I

2. A process according to claim 1, wherein mixture of S,S and S,R-6-t-butoxycarbonyl-hexahydro-1-pyridazinylcarbonyl-1,3-dioxo-2-isoindolebutyric acid is

first treated with ester solvent followed by treatment with an ester solvent and an aliphatic hydrocarbon solvent.

3. A process according to claims 1 or 2, wherein the ester solvent is ethyl acetate, methyl acetate or t-butyl acetate.

4. A process according to claim 3, wherein the ester solvent is ethyl acetate.

5. A process according to claims 1 or 2, wherein the aliphatic hydrocarbon solvent is hexanes, n-pentane or heptane.

6. A process according to claim 5, wherein the aliphatic hydrocarbon solvent is hexanes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/054520

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 C07D487/04
ADD.

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

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 practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 512 924 A (ATTWOOD MICHAEL R [GB] ET AL) 23 April 1985 (1985-04-23) whole document, specially example 1, column 17, lines 22-27 -----	1-6
Y	CA 2 500 558 A1 (APOTEX PHARMACHEM INC [CA]) 10 September 2006 (2006-09-10) whole document, specially stage III (see p. 15) ----- -/--	1-6

☒ 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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search 29 November 2011	Date of mailing of the international search report 06/12/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sahagún Krause, H

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ATTWOOD M R ET AL: "THE DESIGN AND SYNTHESIS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR CILAZAPRIL AND RELATED BICYCLIC COMPOUNDS", JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH; GB, 1 January 1986 (1986-01-01), pages 1011-1019, XP000196065, ISSN: 0300-922X, DOI: 10.1039/P19860001011 schemes 1 and 5 -----	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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